Issued to the Medical Professions only

SUPRANE (desflurane, USP)

PRESENTATION

SUPRANE (desflurane, USP) is a colourless, volatile liquid for inhalation containing 100% desflurane.

INDICATIONS

SUPRANE (desflurane) is indicated as an inhalation agent for induction and/or maintenance of anaesthesia for inpatient and outpatient in adults and maintenance of anaesthesia in infants and children.

DOSAGE AND ADMINISTRATION

SUPRANE (desflurane) is administered by inhalation. The concentration of SUPRANE (desflurane) should be delivered from a vaporiser specifically designed and designated for use with SUPRANE (desflurane). The administration of general anaesthesia must be individualised based on the patient's response.

Opioids or benzodiazepines decrease the amounts of SUPRANE (desflurane) required to produce anaesthesia. SUPRANE (desflurane) decreases the required doses of neuromuscular blocking agents. (See **Table 2**) If added relaxation is required, supplemental doses of muscle relaxants may be used. (See **INTERACTION WITH OTHER MEDICAMENTS AND OTHER FORMS OF INTERACTION**.)

Dosage

The minimum alveolar concentration (MAC) of SUPRANE (desflurane) decreases with increasing patient age. The dose of SUPRANE (desflurane) should be adjusted accordingly. The MAC has been determined as listed in Table 1.

Table 1
MAC for SUPRANE (desflurane) according to patient age and inhalation mixture (Mean ±SD)

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 crossover pairs (using up-and-down method of quantal response).

In patients with coronary artery disease, maintenance of normal haemodynamics is important for avoidance of myocardial ischaemia. SUPRANE (desflurane) should not be used as the sole agent for anaesthetic induction in patients at risk of coronary artery disease or in patients where increases in heart rate or blood pressure are undesirable. It should be used with other medications, preferably intravenous opioids and hypnotics.

Premedication

Issues such as whether or not to premedicate and the choice of premedicant(s) must be individualised. In clinical trials, patients scheduled to be anaesthetised with desflurane frequently received IV pre-anaesthetic medication, such as opioids and/or benzodiazepines.

Induction of Anaesthesia in Adults

In adults, a starting concentration of 3% is recommended, increased in 0.5-1.0% increments every 2 to 3 breaths. Inspired concentrations of 4-11% SUPRANE (desflurane) produce surgical anaesthesia within 2 to 4 minutes. Higher concentrations up to 15% may be used. Such concentrations of SUPRANE (desflurane) will proportionately dilute the concentration of oxygen and commencing administration of oxygen should be 30% or above. During induction in adults, the overall incidence of oxyhaemoglobin desaturation ($SpO_2 < 90\%$) was 6%. High concentrations of SUPRANE (desflurane) may

induce upper airway adverse events. (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 oxygen or nitrous oxide/oxygen.

SUPRANE (desflurane) should be administered at 0.8 MAC or less, and in conjunction with a barbiturate induction and hyperventilation (hypocapnia) until cerebral decompression in patients with known or suspected increases in cerebrospinal fluid pressure (CSFP). Appropriate attention must be paid to maintain cerebral perfusion pressure. (See **SPECIAL WARNINGS AND PRECAUTIONS FOR USE.**)

Induction of Anaesthesia in Children

SUPRANE (desflurane) is not indicated for use as an inhalation induction agent in children and infants because of the frequent occurrence of cough, breath holding, apnoea, laryngospasm and increase in secretions.

Maintenance of Anaesthesia in Adults

SUPRANE (desflurane) at 2.5-8.5% may be required when administered using oxygen or oxygen enriched air. In adults, surgical levels of anaesthesia may be sustained at a reduced concentration of SUPRANE (desflurane) when nitrous oxide is used concomitantly.

Maintenance of Anaesthesia in Children

SUPRANE (desflurane) is indicated for maintenance of anaesthesia in infants and children. Surgical levels of anaesthesia may be maintained in children with end-tidal concentrations of 5.2 to 10% SUPRANE (desflurane) with or without the concomitant use of nitrous oxide.

Although concentrations of up to 18% desflurane have been administered for short periods of time, if high concentrations are used with nitrous oxide it is important to ensure that the inspired mixture contains a minimum of 25% oxygen.

Blood Pressure and Heart Rate During Maintenance

Blood pressure and heart rate should be monitored carefully during maintenance as part of the evaluation of depth of anaesthesia.

Dosage in Renal and Hepatic Impairment

Concentrations of 1-4% SUPRANE (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.

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

CONTRAINDICATIONS
SUPRANE (desflurane) is contraindicated in patients:

- in whom general anaesthesia is contraindicated
- with known sensitivity to halogenated agents.
- with a known or suspected genetic susceptibility to malignant hyperthermia.
- with a history of malignant hyperthermia, or in whom liver dysfunction, jaundice or unexplained fever, leucocytosis, or eosinophilia has occurred after a previous halogenated anaesthetic administration.
- as an inhalation agent in paediatric patients because of the frequent occurrence of cough, breath holding, apnoea, laryngospasm and increased secretions.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Warnings
Malignant Hyperthermia (MH)
In susceptible individuals, potent inhalation anaesthetic agents may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia . SUPRANE (desflurane) was shown to be a potential trigger of malignant hyperthermia. The clinical syndrome is signalled by hypercapnia, and may include muscle rigidity, tachycardia, tachypnoea, cyanosis, arrhythmias, and/or unstable blood pressure. Some of these non-specific signs may also appear under light anaesthesia: acute hypoxia, hypercapnia, and hypovolaemia. Treatment of malignant hyperthermia includes discontinuation of triggering agents, administration of intravenous dantrolene sodium and application of supportive therapy. Renal failure may appear later, and urine flow should be monitored and sustained if possible. SUPRANE (desflurane)

should not be used in subjects known to be susceptible to MH. Fatal outcome of malignant hyperthermia has been reported with desflurane.

Perioperative Hyperkalaemia

Use of inhaled anaesthetic agents, including SUPRANE (desflurane), has been associated with rare increase in serum potassium levels that have resulted in cardiac arrhythmias, some fatal, in patients during 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 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 hyperkalaemia and resistant arrhythmias is recommended, as is subsequent evaluation for latent neuromuscular disease.

Paediatric Inhalation Induction

SUPRANE (desflurane) is not indicated for use as an inhalation induction agent in children and infants because of the frequent occurrence of cough, breath holding, apnoea, laryngospasm and increased secretions.

Use in Children with Bronchial Hypersensitivity

SUPRANE (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.

Maintenance of Anaesthesia in Children

SUPRANE (desflurane) is not approved for maintenance of anaesthesia in non-intubated children under the age of 6 years due to an increased incidence of respiratory adverse reactions. Caution should be exercised when desflurane is used for maintenance anaesthesia with laryngeal mask airway (LMA) in children 6 years old or younger because of the increased potential for adverse respiratory events, e.g. coughing and laryngospasm, especially with the removal of the LMA under deep anaesthesia.

Obstetrics

Due to the limited number of patients studied, the safety of SUPRANE (desflurane) has not been established for use in obstetrics procedures. SUPRANE (desflurane) is a uterine-relaxant and reduces the uterine-placental blood-flow. (See **PREGNANCY AND LACTATION**)

QT Prolongation

QT prolongation, very rarely associated with torsade de pointes, has been reported (see **ADVERSE REACTIONS**).Caution should be exercised when administering desflurane to susceptible patients (e.g., patients with congenital Long QT Syndrome or patients taking drugs that can prolong the QT interval).

Precautions

With the use of halogenated anaesthetics, disruption of hepatic function, icterus and fatal liver necrosis have been reported; such reactions appear to indicate hypersensitivity. SUPRANE (desflurane) may cause sensitivity hepatitis in patients who have been sensitised by previous exposure to halogenated anaesthetics. Cirrhosis, viral hepatitis, or other pre-existing hepatic disease may be a reason to select an anaesthetic other than a halogenated anaesthetic.

SUPRANE (desflurane) may produce a dose-dependent increase CSFP when administered to patients with intra-cranial space occupying lesions. SUPRANE (desflurane) should be administered at 0.8 MAC or less, and in conjunction with a barbiturate induction and hyperventilation (hypocapnia) until cerebral decompression in patients with known or suspected increase in CSFP. Appropriate attention must be paid to maintain cerebral perfusion pressure.

In patients with coronary artery disease, maintenance of normal haemodynamics is important for avoidance of myocardial ischaemia. 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 agent for anaesthetic induction in patients at risk of coronary artery disease or in patients where increases in heart rate or blood pressure are undesirable. It should be used with other medications, preferably intravenous opioids and hypnotics.

During maintenance of anaesthesia, increases in heart rate and blood pressure occurring after rapid incremental increases in end-tidal concentration of SUPRANE (desflurane) may not represent inadequate anaesthesia. 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 anaesthesia.

Hypotension and respiratory depression increases as anaesthesia is deepened.

SUPRANE (desflurane), like some other inhalational anaesthetics, can react with desiccated carbon dioxide (CO_2) absorbents to produce carbon monoxide which may result in elevated levels of carboxyhaemoglobin in some patients. Case reports suggest that barium hydroxide lime and soda lime become desiccated when fresh gases are passed through the CO_2 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 administration of SUPRANE (desflurane).

As with other rapid-acting anaesthetic agents, rapid emergence with SUPRANE (desflurane) should be taken into account in cases where post-anaesthesia pain is anticipated. Care should be taken that appropriate analgesia has been administered to the patient at the end of procedure or early in the post-anaesthesia care unit stay.

Emergence from anaesthesia in children may evoke a brief state of agitation that may hinder cooperation.

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

As with all halogenated anaesthetics repeat anaesthesia within a short period of time should be approached with caution.

Facilities and equipment for maintenance of a patent airway, artificial ventilation, oxygen enrichment and circulatory resuscitation must be immediately available.

INTERACTION WITH OTHER MEDICAMENTS AND OTHER FORMS OF INTERACTION

Concentration of other gases
The MAC for SUPRANE (desflurane) is reduced by concomitant N_2O administration. (see Table 1)

Muscle relaxants
Commonly used muscle relaxants are potentiated by SUPRANE (desflurane).

Anaesthetic concentrations of SUPRANE (desflurane) at equilibrium reduce the ED_{95} of succinycholine by approximately 30% and that of atracurium by approximately 50% compared to N_2O/opioid anaesthesia. The doses of pancuronium, atracurium and suxamethonium needed to produce 95% depression in neuromuscular transmission (ED_{95}) at different concentrations of SUPRANE (desflurane) are reported in **Table 2**. The ED_{95} of vecuronium is 14% lower with desflurane than isoflurane. Additionally,

recovery from neuromuscular blockade is longer with desflurane than with isoflurane.

Table 2: Dosage (mg/kg) of Muscle Relaxant causing 95% Depression in Neuromuscular Transmission

SUPRANE (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

Pre-anaesthetic Drugs

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

Sedatives

Patients anaesthetised with different concentrations of SUPRANE (desflurane) who received increasing doses of intravenous fentanyl or intravenous midazolam showed a reduction in the anaesthetic requirements or MAC. The administration of increasing doses of intravenous midazolam showed a small reduction in MAC. Results are reported in **Table 3**. It is possible that there will be a similar influence on MAC with other opioid and sedative drugs.

Table 3: Effect of Fentanyl or Midazolam on SUPRANE (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

PREGNANCY AND LACTATION

Due to the limited number of patients studied, the safety of SUPRANE (desflurane) has not been established for use in obstetric procedures. SUPRANE (desflurane) is a uterine-relaxant and reduces the uterine-placental blood-flow.

There are no adequate data from the use of SUPRANE (desflurane) in pregnant or lactating women. Physician should carefully consider the potential risks and benefits for each specific patient before prescribing SUPRANE (desflurane) (see **PRECLINICAL SAFETY DATA**).

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There is no information of the effects of SUPRANE (desflurane) following anaesthesia on the ability to operate automobile or heavy machinery. However, patients 0should be advised that the ability to perform such tasks may be impaired after general anaesthesia, and it is advisable to avoid such tasks for a period of 24 hours.

ADVERSE REACTIONS

Adverse Reactions from Clinical Trials

Adverse reactions reported in controlled clinical trials are shown in Tables 4.1 and 4.2. This is an all-patient pooled analysis. The studies were conducted using a variety of premedications, other anaesthetics, and surgical procedures of varying length.

Table 4.1: Clinical Trial Adverse Reactions

Clinical Trial Adverse Reactions		
System Organ Class (SOC)	**Preferred MedDRA Term**	**Frequency**
Induction		
PSYCHIATRIC DISORDERS	**Breath holding**	Common

RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS	**Apnoea** **Laryngospasm** **Hypoxia** **Cough**	Common Common Uncommon Very Common
GASTROINTESTINAL DISORDERS	**Nausea** **Vomiting** **Salivary hypersecretion**	Very Common Very Common Common

Table 4.2: Clinical Trial Adverse Reactions

Clinical Trial Adverse Reactions		
System Organ Class (SOC)	**Preferred MedDRA Term**	**Frequency**
Maintenance or Recovery		
INFECTIONS AND INFESTATIONS	**Pharyngitis**	Common
PSYCHIATRIC DISORDERS	**Agitation** **Breath holding**	Uncommon Common
NERVOUS SYSTEM DISORDERS	**Headache** **Dizziness**	Common Uncommon
EYE DISORDERS	**Conjunctivitis**	Common
CARDIAC DISORDERS	**Nodal arrhythmia** **Bradycardia** **Tachycardia** **Hypertension** **Myocardial infarction** **Myocardial ischaemia** **Arrthymia**	Common Common Common Common Uncommon Uncommon Uncommon
VASCULAR DISORDERS	**Vasodilatation**	Uncommon
RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS	**Apnoea** **Cough** **Hypoxia**	Common Common Uncommon
GASTROINTESTINAL DISORDERS	**Vomiting** **Nausea** **Salivary hypersecretion**	Very Common Very Common Common
MUSCULOSKELETAL, CONNECTIVE TISSUE AND BONE DISORDERS	**Myalgia**	Uncommon
INVESTIGATIONS	**Increased creatinine phosphokinase** **ECG abnormal**	Common Common

ADR frequency is based upon the following scale: Very Common (≥1/10); Common (≥1/100 - <1/10), Uncommon (≥1/1,000 - <1/100), Rare (≥1/10,000 - <1/1,000), Very Rare (<1/10,000)

Post-Marketing Adverse Reactions

In addition to the adverse reactions noted in clinical trials, the following adverse reactions have been reported in the post-marketing experience. These reactions 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: Hyperkalaemia, Hypokalaemia, 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, Haemorrhage, Hypotension, Shock

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS: Respiratory arrest, Respiratory failure, Respiratory distress, Bronchospasm, Haemoptysis

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, Tranaminases increased, Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood bilirubin increased, Coagulation test abnormal, Ammonia increased

INJURY, POISONING, AND PROCEDURAL COMPLICATIONS*: Agitation postoperative, Dizziness*, Migraine*, Tachyarrhythmia*, Palpitations*, Eye burns*, Blindness transient*, Encephalopathy*, Ulcerative keratitis*, Ocular hyperaemia*, Visual acuity reduced*, Eye irritation*, Eye pain*, Fatigue*, Accidental exposure*, Skin burning sensation*, Drug administration error*

*Reaction was due to accidental exposures to non-patients.

Other (Class) Reactions

Other adverse reactions reported with similar products include:
CARDIAC DISORDERS: Electrocardiogram QT prolonged
NERVOUS SYSTEM DISORDERS: Delirium

OVERDOSE

The symptoms of overdosage of SUPRANE (desflurane) can present as a deepening of anaesthesia, 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.

In the event of overdosage or what may appear to be overdosage, the following actions should be taken:

1. Discontinue or minimise exposure to SUPRANE (desflurane)
2. Establish an airway and initiate assisted or controlled ventilation with 100% oxygen.
3. Support and maintain adequate haemodynamics.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Desflurane is one of a family of halogenated methylethylethers which are administered by inhalation producing a dose-related, reversible loss of consciousness and of pain sensations, suppression of voluntary motor activity, modification of autonomic reflexes and sedation of respiration and the cardiovascular system. Other members of the series include enflurane and its structural isomer isoflurane which are halogenated with chlorine as well as fluorine. Desflurane is halogenated exclusively with fluorine. As suggested by its structure, the low blood/gas partition coefficient of desflurane (0.42) is lower than that

of other potent inhaled anaesthetics such as isoflurane (1.4) and even lower than that of nitrous oxide (0.46). Changes in the clinical effects of SUPRANE (desflurane) rapidly follow changes in the inspired concentration. There were no signs of epileptogenic or other untoward effects of EEG, and adjuvant drugs produced no unanticipated or toxic EEG responses during anaesthesia with desflurane. Recovery from anaesthesia was assessed at 30, 60, and 90 minutes following 0.5 MAC desflurane (3%) or isoflurane (0.6%) in N_2O 60% using subjective and objective tests. At 30 minutes after anaesthesia, only 43% of the isoflurane group were able to perform the psychometric tests compared to 76% in the desflurane group ($p < 0.05$).

RECOVERY TESTS: PERCENT OF PREOPERATIVE BASELINE VALUES
16 MALES, 22 FEMALES, AGES 20-65
PERCENT: MEAN ± SD

	60 minutes After Anaesthesia		90 minutes After Anaesthesia	
Maintenance:	**Desflurane/N_2O**	**Isoflurane/N_2O**	**Desflurane/N_2O**	**Isoflurane/N_2O**
Confusion Δ	66 ± 6	47 ± 8	75 ± 7*	56 ± 8
Fatigue Δ	70 ± 9*	33 ± 6	89 ± 12*	47 ± 8
Drowsiness Δ	66 ± 5*	36 ± 8	76 ± 7*	49 ± 9
Clumsiness Δ	65 ± 5	49 ± 8	80 ± 7*	57 ± 9
Comfort Δ	59 ± 7*	30 ± 6	60 ± 8*	31 ± 7
DSST+ score	74 ± 4*	50 ± 9	75 ± 4*	55 ± 7
Trieger Tests++	67 ± 5	74 ± 6	90 ± 6	83 ± 7

Δ Visual analog scale (values from 0-100; 100 = baseline)
+ DSST = Digit Symbol Substitution Test
++ Trieger Test = Dot Connecting Test
* Differences were statistically significant ($p < 0.05$) using a two-sample t-test

SUPRANE (desflurane) was studied in twelve volunteers receiving no other drugs. Haemodynamic effects during controlled ventilation ($PaCO_2$ 38 mm Hg) were:

HAEMODYNAMIC EFFECTS OF DESFLURANE DURING CONTROLLED VENTILATION
12 MALE VOLUNTEERS, AGES 16-26
MEAN ± SD (RANGE)

			Heart Rate (beats/min)		**Mean Arterial Pressure (mm Hg)**		**Cardiac Index ($L/min/m^2$)**	
Total MAC Equivalent	**End-Tidal % Des/O_2**	**End-Tidal % Des/N_2O**	**O_2**	**N_2O**	**O_2**	**N_2O**	**O_2**	**N_2O**
0	0% / 21%	0% / 0%	69 ± 4	70 ± 6	85 ± 9	85 ± 9	3.7 ± 0.4	3.7 ± 0.4
			(63 - 76)	(62 - 85)	(74 - 102)	(74 - 102)	(3.0 - 4.2)	(3.0 - 4.2)
0.8	6% / 94%	3% / 60%	73 ± 5	77 ± 8	61 ± 5*	69 ± 5*	3.2 ± 0.5	3.3 ± 0.5
			(67 - 80)	(67 - 97)	(55 - 70)	(62 - 80)	(2.6 - 4.0)	(2.6 - 4.1)
1.2	9% / 91%	6% / 60%	80 ± 5*	77 ± 7	59 ± 8*	63 ± 8*	3.4 ± 0.5	3.1 ± 0.4*
			(72 - 84)	(67 - 90)	(44 - 71)	(47 - 74)	(2.6 - 4.1)	(2.6 - 3.8)
1.7	12% / 88%	9% / 60%	94 ± 14*	79 ± 9	51 ± 12*	59 ± 6*	3.5 ± 0.9	3.0 ± 0.4*
			(78 - 109)	(61 - 91)	(31 - 66)	(46 - 68)	(1.7 - 4.7)	(2.4 - 3.6)

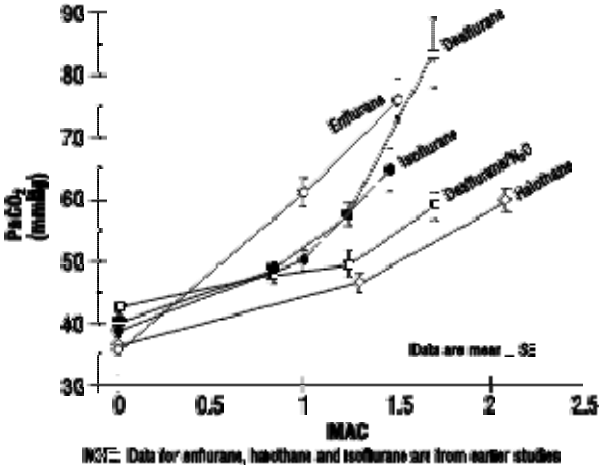
*Differences were statistically significant ($p < 0.05$) compared to awake values, Newman-Keul's method of multiple comparison.

When the same volunteers breathed spontaneously during desflurane anaesthesia, systemic vascular resistance and mean arterial blood pressure decreased; cardiac index, heart rate, stroke volume, and central venous pressure (CVP) increased compared to values when the volunteers were conscious. Cardiac index, stroke volume, and CVP were greater during spontaneous ventilation than during controlled ventilation.

During spontaneous ventilation in the same volunteers, increasing the concentration of SUPRANE (desflurane) from 3% to 12% decreased tidal volume and increased arterial carbon dioxide tension and respiratory rate. The combination of N_2O 60% with a given concentration of desflurane gave results similar to those with desflurane alone. Respiratory depression produced by desflurane is similar to that produced by other potent inhalation agents.

The use of desflurane concentrations higher than 1.5 MAC may produce apnoea.

Figure 1. $PaCO_2$ During Spontaneous Ventilation in Unstimulated Volunteers



The pharmacological effect is proportional to the inspired concentration of SUPRANE (desflurane). The main adverse effects are extensions of the pharmacological action.

PharmacokineticsAs predicted from its physicochemical profile, pharmacokinetic studies in animals as in man indicate that SUPRANE (desflurane) washes into the body more rapidly than other volatile anaesthetics. It also washes out of the body more rapidly allowing quick recovery and flexibility in adjustment of the depth of anaesthesia. SUPRANE (desflurane) is eliminated via the lungs, undergoing only minimal metabolism (0.02%).

Due to the volatile nature of desflurane in plasma samples, the washin-washout profile of desflurane was used as a surrogate of plasma pharmacokinetics. SUPRANE (desflurane) is a volatile liquid inhalation anaesthetic 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). 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 (washin) 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 *(see Figure 2).* The washin rates for halothane and isoflurane were similar to literature values. The washin was faster for desflurane than for isoflurane and halothane at all time points. The F_A/F_{AO} (washout) value at 5 minutes was 0.12 for desflurane, 0.22 for isoflurane, and 0.25 for halothane *(see Figure 3).* The washout 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.

Figure 2. Desflurane Washin

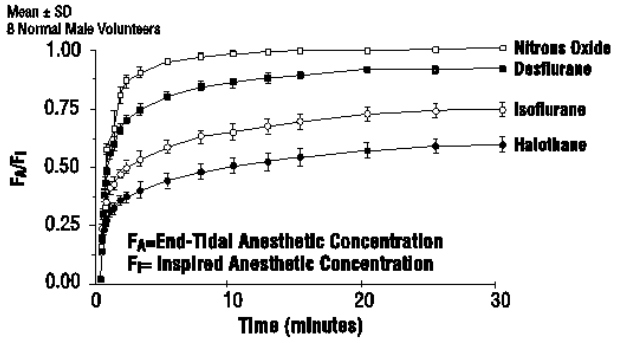
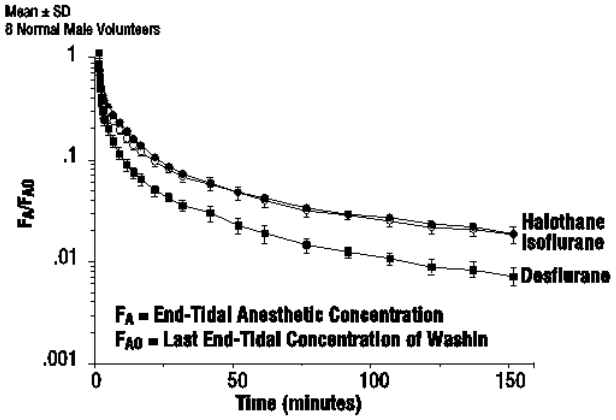


Figure 3. Desflurane Washout



MAC decreases with increasing age. A reduction of dosage is recommended in hypovolaemic, hypotensive and debilitated patients, as discussed under warnings/precautions.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal carcinogenicity studies have not been performed with SUPRANE (desflurane). *In vitro* and *in vivo* genotoxicity studies did not demonstrate mutagenicity or chromosomal damage by desflurane. Tests for genotoxicity included the Ames mutation assay, the metaphase analysis of human lymphocytes, and the mouse micronucleus assay.

Fertility was not affected after 1 MAC-Hour per day exposure (cumulative 63 and 14 MAC-Hours for males and females, respectively). At higher doses, parental toxicity (mortalities and reduced weight gain) was observed which could affect fertility.

PRECLINICAL SAFETY DATA

In swine, desflurane does not sensitize the myocardium to exogenously administered adrenaline. Desflurane appears to produce coronary vasodilatation at arteriolar level in selected animal models, in a similar fashion to that of isoflurane. In an animal model simulating coronary artery disease with conscious, chronically instrumented dogs, desflurane does not appear to divert blood from collateral dependent myocardium to normally perfused areas ("coronary steal"). Clinical studies to date evaluating myocardial ischaemia, infarction and death as outcome parameters have not established that the coronary arteriolar property of SUPRANE (desflurane) is associated with coronary steal or myocardial ischaemia in patients with coronary artery disease.

A detailed experimental program including *in vivo* and *in vitro* studies, did not result in any indication of mutagenic properties of desflurane.

Published animal studies of some anaesthetic/sedation drugs have reported adverse effects on brain development in early life and late pregnancy. These studies have demonstrated that anaesthetic and sedation drugs that block N-methyl-D-aspartate (NMDA) receptors and/or potentiate gamma-aminobutyric acid (GABA) activity during the period of rapid brain growth or synaptogenesis may result in neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis when used for longer than 3 hours. The clinical significance of these non-clinical findings is yet to be determined. However, 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.

CLINICAL STUDIES

The efficacy of SUPRANE (desflurane) was evaluated in 1,843 patients including ambulatory (N=1,061), cardiovascular (N=277), geriatric (N=103), neurosurgical (N=40), and paediatric (N=235) patients. Clinical experience with these patients and with 1,087 control patients in these studies not receiving desflurane is described below. Although desflurane can be used in adults for the inhalation induction of anaesthesia via mask, it produces a high incidence of respiratory irritation (coughing, breath holding, apnoea, increased secretions, laryngospasm). Oxyhaemoglobin saturation below 90% occurred in 6% of patients (from pooled data, N = 370 adults).

Ambulatory Surgery

SUPRANE (desflurane) plus N_2O was compared to isoflurane plus N_2O in multicentre

studies (21 sites) of 792 ASA physical status I, II, or III patients aged 18-76 years (median 32).

Induction

Anaesthetic induction begun with thiopental and continued with desflurane was associated with a 7% incidence of oxyhaemoglobin saturation of 90% or less (from pooled data, N = 307) compared with 5% in patients in whom anaesthesia was induced with thiopental and isoflurane (from pooled data, N = 152).

Maintenance & Recovery

SUPRANE (desflurane) with or without N_2O or other anaesthetics was generally well tolerated. There were no differences between desflurane and the other anaesthetics studied in the times that patients were judged fit for discharge.

In one outpatient study, patients received a standardized anaesthetic consisting of thiopental 4.2-4.4 mg/kg, fentanyl 3.5-4.0 µ g/kg, vecuronium 0.05-0.07 mg/kg, and N_2O 60% in oxygen with either desflurane 3% or isoflurane 0.6%. Emergence times were significantly different; but times to sit up and discharge were not different (see **Table 5**).

TABLE 5
RECOVERY PROFILES AFTER DESFLURANE 3% IN N_2O 60% vs. ISOFLURANE 0.6% IN N_2O 60% IN OUTPATIENTS
16 MALES, 22 FEMALES, AGES 20-65
MEAN ± SD

	Isoflurane	Desflurane
Number	21	17
Anaesthetic time (min)	127 ± 80	98 ± 55
Recovery time to:		
Follow commands (min)	11.1 ± 7.9	6.5 ± 2.3*
Sit up (min)	113 ± 27	95 ± 56
Fit for discharge (min)	231 ± 40	207 ± 54

*Difference was statistically significant from the isoflurane group ($p < 0.05$), unadjusted for multiple comparisons.

Cardiovascular Surgery

Desflurane was compared to isoflurane, sufentanil or fentanyl for the anaesthetic management of coronary artery bypass graft (CABG), abdominal aortic aneurysm, peripheral vascular and carotid endarterectomy surgery in 7 studies at 15 centres involving a total of 558 patients. In all patients except the desflurane vs. sufentanil study,

the volatile anaesthetics were supplemented with intravenous opioids, usually fentanyl. Blood pressure and heart rate were controlled by changes in concentration of the volatile anaesthetics or opioids and cardiovascular drugs if necessary. Oxygen (100%) was the carrier gas in 253 of 277 desflurane cases (24 of 277 received N_2O/O_2).

CARDIOVASCULAR PATIENTS BY AGENT AND TYPE OF SURGERY
418 MALES, 140 FEMALES, AGES 27-87 (MEDIAN 64)

Type of	13 Centres		1 Centre		1 Centre	
Surgery	**Isoflurane**	**Desflurane**	**Sufentanil**	**Desflurane**	**Fentanyl**	**Desflurane**
CABG	58	57	100	100	25	25
Abd Aorta	29	25	-	-	-	-
Periph Vasc	24	24	-	-	-	-
Carotid Art	45	46	-	-	-	-
Total	156	152	100	100	25	25

No differences were found in cardiovascular outcome (death, myocardial infarction, ventricular tachycardia or fibrillation, heart failure) among desflurane and the other anaesthetics.

Induction

SUPRANE (Desflurane) should not be used as the sole agent for anaesthetic induction in patients with coronary artery disease or any patients where increases in heart rate or blood pressure are undesirable. In the desflurane vs. sufentanil study, anaesthetic induction with desflurane without opioids was associated with new transient ischemia in 14 patients vs. 0 in the sufentanil group. In the desflurane group, mean heart rate, arterial pressure, and pulmonary blood pressure increased and stroke volume decreased in contrast to no change in the sufentanil group. Cardiovascular drugs were used frequently in both groups: especially esmolol in the desflurane group (56% vs. 0%) and phenylephrine in the sufentanil group (43% vs. 27%). When 10 µg/kg of fentanyl was used to supplement induction of anaesthesia at one other centre, continuous 2-lead ECG analysis showed a low incidence of myocardial ischaemia and no difference between desflurane and isoflurane. If desflurane is to be used in patients with coronary artery disease, it should be used in combination with other medications for induction of anaesthesia, preferably intravenous opioids and hypnotics.

Maintenance & Recovery

In studies where desflurane or isoflurane anaesthesia was supplemented with fentanyl,

there were no differences in haemodynamic variables or the incidence of myocardial ischemia in the patients anaesthetised with desflurane compared to those anaesthetised with isoflurane.

During the precardiopulmonary bypass period, in the desflurane vs. sufentanil study where the desflurane patients received no intravenous opioid, more desflurane patients required cardiovascular adjuvants to control haemodynamics than the sufentanil patients. During this period, the incidence of ischemia detected by ECG or echocardiography was not statistically different between desflurane (18 of 99) and sufentanil (9 of 98) groups. However, the duration and severity of ECG-detected myocardial ischaemia was significantly less in the desflurane group. The incidence of myocardial ischaemia after cardiopulmonary bypass and in the ICU did not differ between groups.

Geriatric Surgery

SUPRANE (desflurane) plus N_2O was compared to isoflurane plus N_2O in a multicentre study (6 sites) of 203 ASA physical status II or III elderly patients, aged 57-91 years (median 71).

Induction

Most patients were premedicated with fentanyl (mean 2 µg/kg), preoxygenated, and received thiopental (mean 4.3 mg/kg IV) or thiamylal (mean 4 mg/kg IV) followed by succinylcholine (mean 1.4 mg/kg IV) for intubation.

Maintenance & Recovery

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% N_2O. Induction, maintenance, and recovery cardiovascular measurements did not differ from those during isoflurane/N_2O administration nor did the postoperative incidence of nausea and vomiting differ. The most common cardiovascular adverse event was hypotension occurring in 8% of the desflurane patients and 6% of the isoflurane patients.

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.

Induction

Induction consisted of standard neuroanaesthetic techniques including hyperventilation and thiopental.

Maintenance

No change in cerebrospinal fluid pressure (CSFP) was observed in 8 patients who had intracranial tumours when the dose of desflurane was 0.5 MAC in N_2O 50%. In another study of 9 patients with intracranial tumours, 0.8 MAC desflurane /air/O_2 did not increase CSFP above post induction baseline values. In a different study of 10 patients receiving 1.1 MAC desflurane/air/O_2, CSFP increased 7 mm Hg (range 3-13 mm Hg increase, with final values of 11-26 mm Hg) above the pre-drug values.

All volatile anaesthetics may increase intracranial pressure in patients with intracranial space occupying lesions. In such patients, desflurane should be administered at 0.8 MAC or less, and in conjunction with a barbiturate induction and hyperventilation (hypocapnia) in the period before cranial decompression. Appropriate attention must be paid to maintain cerebral perfusion pressure. The use of a lower dose of desflurane and the administration of a barbiturate and mannitol would be predicted to lessen the effect of desflurane on CSFP.

Under hypocapnic conditions ($PaCO_2$ 27 mm Hg) desflurane 1 and 1.5 MAC did not increase cerebral blood flow (CBF) in 9 patients undergoing craniotomies. CBF reactivity to increasing $PaCO_2$ from 27 to 35 mm Hg was also maintained at 1.25 MAC desflurane/air/O_2.

Paediatric Surgery

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

MAINTENANCE IN NONINTUBATED PAEDIATRIC PATIENTS (FACE MASK OR LMA USED; N=300)

All Respiratory Events* (>1% of All Paediatric 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

SUPRANE (desflurane) was associated with higher rates (compared with isoflurane) of coughing, laryngospasm and secretions with an overall rate of respiratory events of 39%. Of the paediatric 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 anaesthesia (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 anaesthesia 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.

PHARMACEUTICAL PARTICULARS

Storage

Store below 30°C.

Store bottle in an upright position. To avoid leakage apply bottle cap firmly to valve, but not too tightly.

SUPRANE (desflurane) must be kept in the original container until immediately prior to use.

SUPRANE (desflurane) is packaged in an amber glass or aluminium bottle containing 240 mL desflurane (depending on the registered container type).This product has a shelf life of 36 months from the date of manufacture.

INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL

Emergency Overview: Concentrations of anaesthetic 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 vapours, 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.

Baxter

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