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

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

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 DESFLURANE decreases with increasing patient age. The dose should be adjusted accordingly (see **WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics**).

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

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 DESFLURANE (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 desflurane in adequately equipped facilities (see **General** section below);
- DESFLURANE (desflurane) can react with desiccated carbon dioxide absorbents to produce carbon monoxide resulting in elevated carboxyhemoglobin levels (see **General** section below);
- DESFLURANE may trigger Malignant Hyperthermia in susceptible individuals and fatal outcomes have been reported (see **Malignant Hyperthermia** section below);
- DESFLURANE use may lead to Perioperative Hyperkalemia in patients with neuromuscular disorders (see **Perioperative Hyperkalemia** section below);
- In pediatric patients, 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
DESFLURANE should be administered only by persons trained in the administration of general anesthesia, using a vaporizer specifically designed and designated for use with 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
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 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 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.

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 DESFLURANE proportionately decreases the concentration of all other gases administered concurrently, including oxygen (O_2). For example, the addition of 10% 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 DESFLURANE required to reach a desired level of anesthesia (see **DOSAGE AND ADMINISTRATION, Table 6**).

Cardiovascular
Caution should be exercised when administering DESFLURANE to susceptible patients. 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 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 desflurane concentration, these increases in heart rate and blood pressure resolve in approximately 4 minutes. At the new, higher end-tidal desflurane concentration blood pressure is likely to be lower and heart rate higher than at the previous, lower steady-state desflurane concentration. The transient increases of heart rate and blood pressure are less if the end-tidal concentration of 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 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 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 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. 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 desflurane alone, without concomitant administration of an opioid, in patients with coronary artery disease, has been associated with an increased incidence of myocardial ischemia. 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 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 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 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; 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 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 DESFLURANE concentration, may be interpreted as light anesthesia. Thus, in such patients, incremental increases of 0.5 – 1.0% end-tidal 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 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):
DESFLURANE anesthesia is contraindicated in subjects known to be susceptible to MH. In susceptible individuals, 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 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 DESFLURANE in patients with pheochromocytoma and neuroblastoma. Since 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
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 desflurane. As with other halogenated anesthetics, 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 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 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 DESFLURANE has not been established and is not recommended for use in neurosurgical procedures (see **CLINICAL TRIALS**).

Special Populations
DESFLURANE 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 DESFLURANE as appropriate to identify potential adverse effects (See **TOXICOLOGY, Reproductive Toxicology**).

Pregnant Women: Due to the limited number of patients studied, the safety of DESFLURANE has not been established for use in obstetric procedures. Volatile inhalational anesthetics, including DESFLURANE, inhibit uterine contraction and reduce uteroplacental blood flow.

There are no adequate data from the use of DESFLURANE in pregnant women.

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

Pediatrics: 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 DESFLURANE and subsequent tracheal intubation, DESFLURANE 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.

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 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 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 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 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 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 desflurane alone and 687 patients were maintained principally with 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
DESFLURANE (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: DESFLURANE (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 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 anaesthetized with desflurane frequently received i.v. pre-anesthetic medication, such as opioids and/or benzodiazepines.
- DESFLURANE (desflurane) is potentiated by benzodiazepines and opioids (see **DRUG INTERACTIONS**).
- Nitrous oxide diminishes the inspired concentration of DESFLURANE required to reach a desired level of anesthesia (see **DOSAGE AND ADMINISTRATION, Table 6**).
- 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**.)
- 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, 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 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. 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 desflurane alone, without concomitant administration of an opioid, in patients with coronary artery disease, has been associated with an increased incidence of myocardial ischemia. 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 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% DESFLURANE with or without the concomitant use of nitrous oxide.

Pediatrics: 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 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% 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 DESFLURANE will usually be within 10% of the inspired concentration.

During the maintenance of anesthesia, increasing concentrations of 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 DESFLURANE.

Concentrations of 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 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 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 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; 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 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 DESFLURANE concentration may be interpreted as light anesthesia. Thus, in such patients, incremental increases of 0.5-1.0% end-tidal 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
DESFLURANE is administered by inhalation. Deliver DESFLURANE from a vaporizer specifically designed and designated for use with desflurane. A Blue-Zone screw-on bottle Adapter is provided to allow safe transfer of DESFLURANE into an anesthetic Desflurane vaporizer. The desflurane bottle must be maintained between 4 – 10°C before setting up the Blue-Zone bottle adapter on the bottle. This procedure should only be done sufficiently close to an active scavenger opening. The adequacy of the seal between the adapter and the bottle must be verified before fitting the bottle and adapter combination on to the vaporizer for filling.

The administration of general anesthesia must be individualized based on the patient's response.

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**).

DESFLURANE (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 mcg/kg), alfentanil (10 or 20 mcg/kg), or clonidine 4 mcg/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 mcg/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_{A0} (*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_{A0} 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, e.g. 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 ± 1.6L
4th Compartment	11 ± 3 L
Fat Group	2.1 ± 0.4L

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, desflurane 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**).

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 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
Preserve in tight, light-resistant containers stored upright between 15-25°C.

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
DESFLURANE (desflurane) is supplied in 250 mL amber glass bottles, containing 180 mL desflurane at 100% v/v concentration. Each carton contains six bottles and these are co-packaged with six Blue-Zone bottle Adapters.

MORE INFORMATION
This leaflet was prepared by

blue zone®

Blue-Zone Technologies Ltd.
Concord, Ontario, Canada, L4K 3C1

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This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Blue-Zone Technologies Ltd., at 1-844-761-1224.