AUSTRALIAN PRODUCT INFORMATION – PIRAMAL DESFLURANE™ (DESFLURANE)

1. NAME OF THE MEDICINE

Desflurane

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient of PIRAMAL DESFLURANE is 1 mL/mL desflurane.
List of excipients: None

3. PHARMACEUTICAL FORM

Liquid for inhalation

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

PIRAMAL DESFLURANE™ is indicated as an inhalation agent for maintenance of anaesthesia. DESFLURANE is not recommended for mask induction of anaesthesia because of a high incidence of moderate to severe upper airway adverse events.

4.2. DOSE AND METHOD OF ADMINISTRATION

DESFLURANE is administered by inhalation. The concentration of DESFLURANE should be administered by persons trained in the administration of general anaesthesia and delivered from a vaporiser specifically designed and designated for use with DESFLURANE (see **4.4 Special Warnings and Precautions for use**).

The vapour pressure of DESFLURANE at room temperature (about 700 mm Hg) precludes its use in commonly-used agent-specific vaporisers as such vaporisers cannot provide a stable and predictable delivered concentration. Unlike agent-specific vaporisers, DESFLURANE requires a vaporiser which utilises a heated sump (enclosure containing liquid desflurane) to prevent condensation, which could occur should the temperature in the sump fall below 22.8°C at 1 atmosphere pressure (desflurane boiling point). To power the heating elements, the vaporiser must be connected to an electrical source. A vaporiser designed for use with DESFLURANE must also include a filling port compatible with the valve on the DESFLURANE bottle.

Premedication

The premedication should be chosen to suit the individual requirements of the patient. Studies to date with patients scheduled to be anaesthetised have frequently received IV premedication such as opioids and/or benzodiazepines, and these have not shown an effect of premedication on respiratory tract reactions associated with inhalational induction of anaesthesia.

Dosage

The minimum alveolar concentration (MAC) of DESFLURANE is age-specific and decreases with increasing patient age. The administration of general anaesthesia must be individualised based on the patient's response, thus the dose of DESFLURANE should be adjusted accordingly individually. The MAC has been determined as listed in Table 1 below (see **5.2 Pharmacokinetic Properties**):

Table 1: Effect of Age on DESFLURANE MAC

AGE	**100% OXYGEN (end-tidal %)**	**60% NITROUS OXIDE/ 40% OXYGEN (end-tidal %)**
0 – 1 year	8.95 – 10.65	5.75 – 7.75*
1 – 12 years	7.20 – 9.40	5.75 – 7.00**
18 – 30 years	6.35 – 7.25	3.75 – 4.25
30 – 65 years	5.75 – 6.25	1.75 – 3.25
Over 65 years	5.17 ± 0.6%	1.67 ± 0.4%

*3 – 12 months **1 – 5 Years

The MAC for desflurane is reduced by concomitant N_2O administration.

Opioids or benzodiazepines decrease the amounts of DESFLURANE required to produce anaesthesia. DESFLURANE decreases the doses of neuromuscular blocking agents (see **4.5 Interactions With Other Medicines And Other Forms of Interactions**).

In patients with coronary artery disease, maintenance of normal haemodynamics is important to avoid myocardial ischaemia. DESFLURANE should not be used as the sole anaesthetic in patients with coronary artery disease or in patients where increases in heart rate or blood pressure are undesirable. Thus, when DESFLURANE is to be used in patients with coronary artery disease, it should always be used in combination with other medicines, such as intravenous opioids or hypnotics and it should not be used for induction (see **4.4 Special Warnings And Precautions For Use**).

Induction

DESFLURANE is not recommended for induction of general anaesthesia (see **4.3 Contraindications and 4.4 Special Warnings And Precautions For Use)** via mask because of the high incidence of upper airway adverse events such as laryngospasm, apnoea, increase in secretions, breath- holding and coughing, especially in children and infants and with high concentrations of DESFLURANE.

After induction in adults with an intravenous drug such as thiopental or propofol, DESFLURANE can be started at approximately 0.5 to 1 MAC, whether the carrier gas is O_2 or N_2O/O_2.

In patients with known or suspected increases in cerebrospinal fluid pressure, desflurane should be administered at 0.8 MAC or less in conjunction with a barbiturate or propofol induction and hyperventilation (hypocapnia) in the period before cranial decompression. Appropriate attention must be paid to maintain cerebral perfusion pressure (see **CLINICAL TRIALS,** ***Neurosurgery*** and **4.4 Special Warnings And Precautions For Use**).

Maintenance

Surgical levels of anaesthesia may be sustained with 2 to 6% end-tidal concentration of DESFLURANE when N_2O is used concomitantly. DESFLURANE at 2.5 to 8.5% end-tidal concentration may be required when administered using O_2 or oxygen enriched air.

In children, surgical levels of anaesthesia may be maintained with end-tidal concentrations of 5.2 to 10% DESFLURANE with or without the concomitant use of N_2O. Although end-tidal concentrations of up to 18% desflurane have been administered for short periods of time, if high concentrations are used with N_2O, it is important to ensure that the inspired mixture contains a minimum of 25% O_2.

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

If added relaxation is required, supplemental doses of muscle relaxants may be used.

Dosage in Renal and Hepatic Impairment

End-tidal concentrations of 1 to 4% DESFLURANE in N_2O/O_2 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.

4.3. CONTRAINDICATIONS

DESFLURANE should not be used for patients in whom general anaesthesia is contraindicated. DESFLURANE is also contraindicated in patients with known sensitivity to halogenated agents and in patients with known or genetic susceptibility to malignant hyperthermia. DESFLURANE is also contraindicated in patients with a history of malignant hyperthermia, or in whom liver dysfunction, hepatitis or jaundice with unexplained fever, leucocytosis and/or eosinophilia has occurred after a previous halogenated anaesthetic administration.

DESFLURANE is contraindicated for use as an inhalation induction agent in paediatric patients because of the frequent occurrence of cough, breath-holding, apnoea, laryngospasm and increased secretions.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

DESFLURANE is not recommended for use as an inhalation induction agent in adults, children and infants (see **4.3 Contraindications**) because of the frequent occurrence of cough, breath-holding, apnoea, laryngospasm and increased secretions.

DESFLURANE, as with other halogenated anaesthetics, has been reported to interact with dry carbon dioxide (CO_2) absorbents to form carbon monoxide that 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 absorber canister at high flow rates over many hours or days, or after the machine has been idle for two or more days. An ex-vivo study suggests that barium hydroxide lime has greater potential for carbon monoxide production but the phenomenon may also occur with dried soda lime when fresh gases are passed through the CO_2 canister at high flow rate over many hours or days. In order to minimise the risk of formation of carbon monoxide in rebreathing circuits and the possibility of elevated carboxyhaemoglobin levels, fresh (moist) CO_2 absorbents should be used. The moisture content of soda lime should always be ≥5% water, and that of Baralyme, ≥10% water. When the anaesthetist has any doubt regarding the moisture content of the CO_2 absorbent, or suspects that the CO_2 absorbent may be desiccated, it should be replaced before administration of DESFLURANE.

In addition, consideration should be given to direct measurement of carboxyhaemoglobin levels in patients on closed circuit anaesthesia with desflurane, if oxygen desaturation develops which does not respond to usual corrective steps.

Fluoroform is another degradation product. Adequate data on the toxicology of fluoroform are not available.

As with other rapid-acting anaesthetic agents, rapid emergence with 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 the procedure or early in the post-anaesthesia care unit stay.

There is insufficient experience of use in repeated anaesthesia to make a definite recommendation in this regard. As with all halogenated anaesthetics, repeat anaesthesia within a short period of time should be approached with caution.

In healthy volunteers, in the absence of concomitant N_2O and/or opioid administration, sudden step increases in the inspired concentration of DESFLURANE may cause transient increases in sympathetic activity with associated increases in heart rate and blood pressure. The haemodynamic 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 inspired 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 inspired concentration of DESFLURANE is increased in increments of 1% or less. However, if during the transiently increased heart rate and blood pressure end-tidal concentration of DESFLURANE is again 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 lignocaine or by intravenous propofol.

During maintenance of anaesthesia, increases in heart rate and blood pressure occurring after rapid incremental increases in end-tidal concentration of 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 DESFLURANE concentration may be interpreted as light anaesthesia. Thus, in such patients, incremental increases of 0.5-1.0% end-tidal DESFLURANE may attenuate these signs of light anaesthesia, as may concomitant administration of analgesics. Should raised heart rate and blood pressure persist, then other causes should be

sought.

Hypotension and respiratory depression increase as anaesthesia is deepened.

When changing the depth of anaesthesia, rapid increases in the end-tidal concentration of DESFLURANE should be avoided and the end-tidal concentration increased in small amounts of 1% or less. It is not necessary to deliver concentrations of DESFLURANE far in excess of the desired end-tidal concentration ("overpressurisation" 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.

In patients with coronary artery disease, maintenance of normal haemodynamics is important to avoid myocardial ischemia. DESFLURANE should not be used as the sole anaesthetic in patients with coronary artery disease or in patients where increases in heart rate or blood pressure are undesirable. Rapid inhaled induction of anaesthesia with DESFLURANE alone, without concomitant administration of an opioid, in patients with coronary artery disease, has been associated with an increased incidence of myocardial ischaemia, marked increases in pulse rate, increases in mean arterial pressure and increases in adrenaline and noradrenaline levels. DESFLURANE, when given in conjunction with opioids for maintenance of anaesthesia in patients with coronary artery disease, has not produced an incidence of ischaemia different from that produced by other anaesthetics. Thus, when DESFLURANE is to be used in patients with coronary artery disease, it should always be used in combination with other medicaments, such as intravenous opioids or hypnotics and it should not be used for induction.

DESFLURANE, as with other volatile anaesthetics, may produce a dose-dependent increase in cerebrospinal fluid (CSF) or intracranial pressure in patients with space occupying lesions. In such patients, desflurane should be administered at 0.8 Minimum Alveolar Concentration (MAC) or less, and in conjunction with a barbiturate or propofol induction and hyperventilation (hypocapnia) in the period before cranial decompression. Appropriate attention must be paid to maintain cerebral perfusion pressure.

Use of DESFLURANE in hypovolaemic, hypotensive and debilitated patients has not been extensively investigated. As with other potent inhaled anaesthetics, a lower concentration is recommended for use in these patients.

As with other agents of this type, DESFLURANE was shown to be a potential trigger of a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as of malignant hyperthermia (MH). The syndrome includes non-specific features such as hypercapnia, muscle rigidity, tachycardia, tachypnoea,

cyanosis, arrhythmias and/or unstable blood pressure and an increase in overall metabolism may be reflected in an elevated temperature. Some of these non-specific signs may also appear during light anaesthesia: acute hypoxia, hypercapnia and hypervolaemia. If malignant hyperthermia occurs, discontinue triggering agent(s). Administration of intravenous dantrolene sodium will be indicated to reverse this hyperthermia, as well as application of supportive therapy. DESFLURANE should not be used in subjects known to be susceptible to MH (see **4.3 Contraindications** and **4.8 Adverse Effects (Undesirable Effects)**). 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.

Due to limited experience in obstetric operations, including termination of pregnancy, DESFLURANE cannot be recommended for this type of surgery. Desflurane is a uterine-relaxant and reduces the uterine-placental blood-flow (see **Use in Pregnancy**).

DESFLURANE should not be used in patients in whom liver dysfunction, unexplained fever or leucocytosis has occurred after a previous halogenated anaesthetic administration. With the use of halogenated anaesthetics, disruption of the liver function, jaundice and fatal liver necrosis have been reported. Such reactions appear to indicate hypersensitivity reactions to anaesthetics. Desflurane may cause sensitivity hepatitis in patients who have been sensitised by previous exposure to halogenated anaesthetics. Cirrhosis, viral hepatitis, or other pre-existing liver disease can be a reason to select an anaesthetic other than a halogenated anaesthetic.

As with other halogenated anaesthetics agents, desflurane has been associated with some elevation of glucose intra-operatively.

Use of inhaled anaesthetic 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 hyperkalaemia and resistant arrhythmias is recommended, as is subsequent evaluation for latent neuromuscular disease.

Use in the elderly

The minimum alveolar concentration (MAC) of DESFLURANE is age-specific and decreases with increasing patient age. The administration of general anaesthesia must

be individualised based on the patient's response, thus the dose of DESFLURANE should be adjusted accordingly individually. Refer to **Table 1, section 4.2 Dose and Method of Administration**.

Paediatric use

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, eg. coughing and laryngospasm, especially with removal of the LMA under deep anaesthesia.

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

Paediatric Neurotoxicity

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

Published animal studies of some anaesthetic/analgesic/sedation drugs have reported adverse effects on brain development in early life and late pregnancy. The clinical significance of these nonclinical finding is yet to be determined.

With inhalation or infusion of such drugs, exposure is longer than the period of inhalation or infusion. Depending on the drug and patient characteristics, as well as dosage, the elimination phase may be prolonged relative to the period of administration.

QT Prolongation

QT prolongation, very rarely associated with torsade de pointes, has been reported (see **4.8 Adverse Effects (Undesirable Effects)**). Caution should be exercised when administering desflurane to susceptible patients.

Effects on laboratory tests

The effect of this medicine on laboratory tests has not been established.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

Non depolarising and depolarising muscle relaxants

Commonly used muscle relaxants are potentiated by DESFLURANE. Anaesthetic concentrations of desflurane at equilibrium reduce the ED_{95} of succinylcholine by approximately 30% and that of atracurium and pancuronium by approximately 50% compared to N_2O/opioid anaesthesia. The doses of pancuronium, atracurium, suxamethonium and vecuronium needed to produce 95% (ED_{95}) depression in neuromuscular transmission at different concentrations of DESFLURANE are given in Table 2. With the exception of vecuronium, these doses are similar to isoflurane. 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 of Muscle Relaxant Causing 95% Depression in Neuromuscular Transmission at Common DESFLURANE Concentrations

DESFLURANE Concentration	**Mean ED_{95} (mg/kg)**			
	Pancuronium	Atracurium	Suxamethonium	Vecuronium
0.65 MAC/60% N_2O/O_2	0.026	0.133	*NA	*NA
1.25 MAC/60% N_2O/O_2	0.018	0.119	*NA	*NA
1.25 MAC/100% O_2	0.022	0.120	0.360	0.019

*NA = Not Available; MAC= Minimum Alveolar Concentration

Opioids and benzodiazepines

Lower doses of DESFLURANE are required in patients receiving opioids, benzodiazepines or other sedatives. These interactions are illustrated below. In addition, concomitant nitrous oxide reduces DESFLURANE MAC, as illustrated under dosage, below. Patients anaesthetised with different concentrations of DESFLURANE who received increasing doses of intravenous fentanyl or intravenous midazolam showed a marked 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. These MAC reductions are similar to those observed with isoflurane. It is anticipated that there will be a similar influence on MAC with other opioid and sedative drugs.

Table 3: Effect of Fentanyl or Midazolam on DESFLURANE MAC

	*MAC (end-tidal %)	% MAC reduction
No Fentanyl	6.33 – 6.35	-
Fentanyl (3µg/kg)	3.12 – 3.46	46 – 51
Fentanyl (6µg/kg)	2.25 – 2.97	53 – 64
No Midazolam	5.85 – 6.86	-
Midazolam (25µg/kg)	4.93	15.7
Midazolam (50µg/kg)	4.88	16.6

*Includes value for ages 18 – 65 years

Concentration of other gases
The MAC for desflurane is reduced by concomitant N_2O administration (see **4.2 Dose and Method of Administration**).

Glucose elevation
As with other halogenated anaesthetics agents, desflurane has been associated with some elevation of glucose intra-operatively (see **4.4 Special Warnings and Precautions For Use**).

See **6.2 INCOMPATIBILITIES.**

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
Studies in rats showed a slight reduction in male fertility and pregnancy rates after exposure to desflurane at exposures producing parental toxicity (mortalities and reduced weight gain). Fertility was not affected after 1 MAC hour per day desflurane exposure (cumulative 63 and 14 MAC hours for males and females respectively).

Use in pregnancy
Category B3 - No teratogenic effect was observed in rats or rabbits at approximately 40 cumulative MAC hour desflurane exposures during organogenesis. At this cumulative anaesthetic exposure an increase in foetal death (post-implantation loss) was observed in rats but not rabbits. These effects were observed at exposures producing a significant reduction in maternal body weight gain.

No studies of peri/post-natal physical and functional development following maternal exposures to desflurane have been conducted in animals, but a limited study in rats showed offspring body weight to be reduced by 12-18% over the lactation period (day 0-21 post-partum) following maternal exposure to 1 MAC desflurane for 4 h/day from day 15 of gestation to day 21 of lactation.

Published animal studies of some anaesthetic/analgesic/sedation drugs have reported adverse effects on brain development in early life and late pregnancy.

In published fetal rhesus macaque studies, isoflurane exposed in utero, resulted in increased neuronal and oligodendrocyte apoptosis in the developing brain of the offspring. Studies in juvenile animals suggest neuroapoptosis correlates with long-term cognitive deficits.

Published studies in pregnant and juvenile animals demonstrate that the use of anaesthetic/analgesic and sedation drugs that block NMDA receptors and/or potentiate GABA activity during the period of rapid brain growth or synaptogenesis may result in neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis when used for longer than 3 hours. These studies included anaesthetic agents from a variety of drug classes.

There are no adequate and well-controlled studies in pregnant women. As desflurane is a uterine relaxant and reduces the uterine-placental blood flow, and safety has not been established for use in obstetric procedures, DESFLURANE should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use in lactation

There are no adequate data in lactating women. DESFLURANE is not indicated for use in nursing mothers because it is not known whether it is excreted in human milk.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There is no information of the effects of DESFLURANE on the ability to drive or operate machinery. However, patients should be advised that the ability to perform tasks such as driving or operation of machinery may be impaired after general anaesthesia, and it is advisable to avoid such tasks for a period of 24 hours.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

As with all potent inhaled anaesthetics, DESFLURANE may cause dose-dependent hypotension. A dose-dependent respiratory depression is also observed. Most other adverse events are mild and transient.

Desflurane is not recommended for use as an inhalational induction agent because of the frequent occurrence of cough, breath holding, apnoea, laryngospasm and increased secretions.

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

patient's response to the surgical procedure.

Adverse event information is derived from controlled clinical trials. The studies were conducted using a variety of premedications, other anaesthetics, 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 common adverse reactions (>1% occurrence) below, 370 adults and 152 children in whom anaesthesia was induced with DESFLURANE alone and 687 patients in whom anaesthesia was 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 presented in alphabetical order within each body system.

PROBABLY CAUSALLY RELATED:

Incidence > 10%

Induction (use as a mask inhalation agent):

Adult patients (N=370)

Psychiatric Disorders:	breath-holding 27%
Respiratory, Thoracic, and Mediastinal disorders:	coughing 34%, apnoea 15%

Paediatric patients (N=152):

Psychiatric Disorders:	breath-holding 68%, laryngospasm 50%
Respiratory, Thoracic, and Mediastinal Disorders:	coughing 72%, oxygen saturation decreased (SpO2<90%) 26%, laryngospasm 50%
Gastrointestinal Disorders:	salivary hypersecretion 21%, nausea, vomiting

Maintenance or Recovery

Adult and paediatric patients (N=687):

Cardiac Disorders:	nodal arrhythmia, bradycardia, tachycardia, hypertension
Vascular Disorders:	hypertension
Gastrointestinal Disorders:	nausea 27%, vomiting 16%

Incidence 1-10%

Induction (use as a mask inhalation agent):

Adult patients (N=370):

Infections and Infestations:	Pharyngitis 4%
Respiratory, Thoracic, and Mediastinal Disorders:	Oxygen saturation decreased (SpO_2<90%) 8%, laryngospasm 8%
Gastrointestinal Disorders:	Salivary hypersecretion 9%

Paediatric patients (N=152):

Respiratory, Thoracic, and Mediastinal Disorders:	bronchospasm 3%

Maintenance or Recovery

Adult and paediatric patients (N=687):

Infections and Infestations:	pharyngitis 1%
Psychiatric Disorders:	breath-holding 2%
Nervous System Disorders:	salivary hypersecretion 1%
Respiratory, Thoracic, and Mediastinal Disorders:	apnoea 7%, cough 4%, laryngospasm 3%
Body as a Whole:	headache 1%
Special Senses:	conjunctivitis (conjunctival hyperaemia) 2%
Investigations:	increased creatinine phosphokinase, Electrocardiogram abnormal

Incidence <1% and reported in 3 or more patients, regardless of severity (N=1,843)

Nervous System Disorders:	agitation, dizziness
Cardiac Disorders:	arrhythmia, bigeminy, myocardial ischaemia, Vasodilation
Respiratory, Thoracic, and Mediastinal Disorders:	asthma, dyspnoea, hypoxia
Vascular Disorders:	vasodilation

CAUSAL RELATIONSHIP UNKNOWN:

Incidence <1% and reported in 3 or more patients, regardless of severity (N=1,843)

Cardiac Disorders:	haemorrhage, myocardial infarction
Musculoskeletal System:	myalgia
Skin and Appendages:	pruritus
Body as a Whole:	fever

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.

BLOOD AND LYMPHATIC SYSTEM DISORDERS: Coagulopathy

METABOLISM AND NUTRITION DIOSORDERS: Hyperkalaemia, Hypokalaemia, Metabolic acidosis

NERVOUS SYSTEM DISORDERS: Convulsion, Dizziness, Migraine

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, laryngospasm, Respiratory failure, Hypoxia, respiratory distress, Bronchospasm, Haemoptysis

GASTROINTESTINAL DISORDERS: Pancreatitis acute, Abdominal pain

HEPATOBILIARY DISORDERS: Hepatic failure, Hepatic necrosis, Hepatitis[1], 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, Asthaenia, 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 * : 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

** All of the reactions categorised within this SOC were accidental exposure to non-patients.*

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

Laboratory Findings: Transient elevations in glucose and white blood cell count may occur as with the use of other anaesthetic agents. Abnormal liver function tests were observed in <1% of patients.

Hepatitis has been reported very rarely <0.0001%[1].

A comparison of the adverse events most frequently reported for desflurane and its main comparator in the controlled clinical trials, isoflurane, can be found in Table 4 below. With the exception of respiratory complications (primarily occurring during the induction period), adverse event rates are comparable.

Table 4: Comparison of Adverse Events: Desflurane and Isoflurane (Most Frequently Reported Events)

Event	Desflurane N=1843	Isoflurane N=626
Nausea	23%	17%
Respiratory Disorder (breathholding)	16%	<1%
Cough Increased	15%	<1%
Vomiting	13%	10%
Apnoea	9%	0%
Laryngismus	8%	2%
Bradycardia	2%	1%
Conjunctival hyperaemia	2%	0%
Hypotension	2%	4%
Tachycardia	2%	1%
Headache	1%	<1%
Hypertension	1%	1%
Nodal Arrhythmia	1%	0%
Pharyngitis	1%	<1%
Arrhythmia	<1%	<1%
Asthma	<1%	<1%
Creatinine Phosphokinase increased	<1%	<1%
Dizziness	<1%	<1%
Increased Salivation	<1%	0%
Nausea and Vomiting	<1%	1%

As with other agents of this type, desflurane anaesthesia has been shown to trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia (see **4.4 Special Warnings and Precautions For Use)**. The syndrome includes non-specific features such as hypercapnia, muscle rigidity, tachycardia, tachypnoea, cyanosis, arrhythmias and unstable blood pressure and an increase in overall metabolism may be reflected in an elevated temperature. Some of these non-specific signs may also appear during light anaesthesia: acute hypoxia, hypercapnia and hypervolemia. Renal failure may appear later.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting- problems.

4.9 OVERDOSE

Human experience
There is no experience of overdosage in humans.

Symptoms and treatment of overdosage
The symptoms of overdosage of DESFLURANE are anticipated to be similar to those of other volatile agents with a deepening of anaesthesia, cardiac and/or respiratory depression in spontaneous 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: stop DESFLURANE, establish a clear airway and initiate assisted or controlled ventilation with pure oxygen and support and maintain adequate haemodynamics.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Mechanism of action
Desflurane is one of a family of halogenated methyl ethyl ethers which is 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. Consistent with its high degree of fluorination, desflurane exhibits very low solubility in water with a corresponding low blood/gas partition coefficient. 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 DESFLURANE rapidly follow changes in the inspired concentration. These data explain the rapid washout with desflurane anaesthesia, but clinical studies have not shown a faster time to hospital discharge when desflurane was compared with related agents. Animal studies showed a more rapid induction and recovery from anaesthesia than for isoflurane, with a similar cardiorespiratory profile. 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.

Studies in pigs bred to be susceptible to malignant hyperthermia (MH) indicated that DESFLURANE is a potential trigger for MH.

The pharmacological effect is proportional to the inspired concentration of DESFLURANE. The main adverse effects are extensions of the pharmacological action.

CLINICAL TRIALS

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

Ambulatory Surgery

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

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 (ASA physical status II, III and IV).

Cardiac Studies

The effects of DESFLURANE in patients undergoing CABG surgery were investigated in three studies.

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

sufentanil group had myocardial ischaemia of greater duration and intensity than did the DESFLURANE group. There were no differences in incidence of myocardial infarction or death between the two groups.

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

In the third study, investigators compared DESFLURANE with isoflurane in groups of 57 and 58 patients, respectively. Both groups were given up to 10 µg/kg fentanyl during induction of anaesthesia. The mean end-tidal anaesthetic concentrations prior to coronary bypass were 6% DESFLURANE or 0.9% isoflurane. DESFLURANE and isoflurane provided clinically acceptable anaesthesia prior to and after coronary bypass. A sub-analysis was performed for data collected at one of the study centres. At this centre DESFLURANE was administered to 21 patients and 20 patients received isoflurane. Both groups were given fentanyl 10 µg/kg; during induction of anaesthesia the maximum end-tidal anaesthetic concentrations were 6% DESFLURANE or 1.4% isoflurane. The groups had similar incidence of ischaemia (as detected by Holter monitoring), myocardial infarction, and death.

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

Peripheral Vascular Studies

Four randomised, open-label trials were conducted to assess the haemodynamic stability of patients administered DESFLURANE versus isoflurane for maintenance of anaesthesia in peripheral vascular surgeries. These studies are summarised in Table 5 below.

Table 5: Summary of Doses in Peripheral Vascular Surgery Studies

Type of Surgery	Desflurane/O_2		Isoflurane/O_2	
	N	**Mean End-tidal Concentrations (%)**	**N**	**Mean End-tidal Concentrations (%)**
Abdominal aorta	25	5.2	29	0.74
Peripheral vascular	24	2.9*	24	0.43*
Carotid endarterectomy	31	4.4	30	0.7
	15	6.1	15	0.65

* Desflurane and isoflurane administered with 60% N_2O

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

DESFLURANE should not be used as the sole anaesthetic in patients with coronary artery disease or in patients where increases in the heart rate or blood pressure are undesirable (see **4.4 Special Warning and Precautions for use**).

Geriatric Surgery

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

Neurosurgery

DESFLURANE was administered to 56 patients aged 26-77 (median 48 years), ASA physical status II or III undergoing neurosurgical procedures for intracranial lesions. A further 59 patients are reported in the literature. All volatile anaesthetics may increase intracranial pressure in patients with space occupying lesions. In such patients, desflurane should be administered at 0.8 MAC or less in conjunction with a barbiturate or propofol 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.

Paediatric Surgery
DESFLURANE was compared to halothane, with or without nitrous oxide, in 323 patients aged 2 weeks to 12 years (median 2 years), ASA physical status I or II.

DESFLURANE is not suitable for induction of anaesthesia in children and infants. Induction of anaesthesia with DESFLURANE demonstrated an unacceptably high incidence of coughing (72%), breath-holding (68%), laryngospasm (50%), secretions (21%) and apnoea. The occurrence of oxyhaemoglobin desaturation was 26%. Premedication did not have an effect on tempering these upper airway responses to DESFLURANE induction.

The concentration of DESFLURANE required for maintenance of anaesthesia is age dependent (see **4.2 Dose and Method of Administration**). Changes in blood pressure during maintenance of and recovery from anaesthesia were similar between DESFLURANE/N_2O/O_2 and halothane/N_2O/O_2. Heart rate during maintenance of anaesthesia was approximately 10 beats/min faster with DESFLURANE than with halothane. Patients were judged fit for discharge from post-anaesthesia care units within one hour with both DESFLURANE and halothane. There were no differences in the incidence of nausea and vomiting between DESFLURANE and halothane.

Obstetric Surgery
DESFLURANE was studied in a total of 133 ASA physical status I or II patients for analgesia during vaginal delivery, anaesthesia for Caesarean section and elective D&C for termination of pregnancy. Due to the limited number of patients studied, the safety of DESFLURANE has not been established for use in obstetric procedures (see **Use in Pregnancy)**.

5.2 PHARMACOKINETIC PROPERTIES

As predicted from its physiochemical profile, pharmacokinetic studies in animals as in man indicate that DESFLURANE washes into the body more rapidly than other volatile anaesthetics (see Figure 1). It also washes out of the body more rapidly allowing quick recovery and flexibility in adjustment of the depth of anaesthesia (see Figure 2). DESFLURANE is eliminated via the lungs, undergoing only minimal metabolism (0.02%).

Figure 1. Desflurane Washing

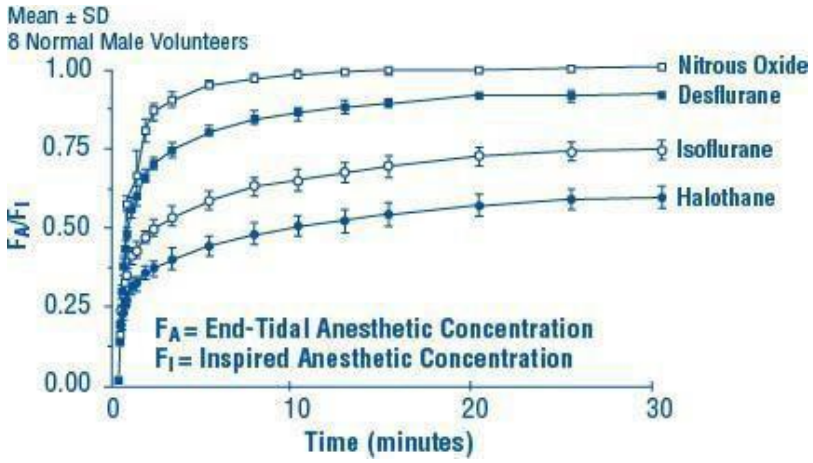
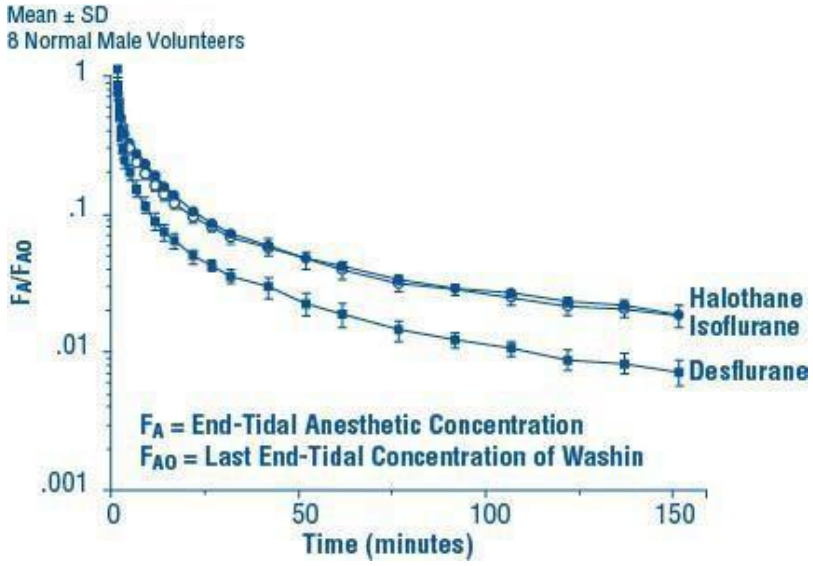


Figure 2. Desflurane Washout



Minimum Alveolar Concentration (MAC) decreases with increasing age. A reduction of dosage is recommended in hypovolaemic, hypotensive and debilitated patients, as discussed under Special Warnings and Special Precautions.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Desflurane did not show evidence of genotoxicity in assays for gene mutations and chromosomal damage.

Carcinogenicity
No studies on the potential carcinogenic activity of desflurane have been conducted

Preclinical Safety Data
The potential for desflurane to sensitise the myocardium to exogenously administered adrenaline is similar to that of isoflurane in swine. Desflurane appears to produce coronary vasodilation 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 DESFLURANE is associated with coronary steal or myocardial ischaemia in patients with coronary artery disease.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

None

6.2 INCOMPATIBILITIES

DESFLURANE has been reported to interact with dry carbon dioxide (CO_2) absorbents to form carbon monoxide that may result in elevated levels of carboxyhemoglobin in some patients.

In order to minimise the risk of formation of carbon monoxide in rebreathing circuits and the possibility of elevated carboxyhaemoglobin levels, fresh (moist) carbon dioxide absorbents should be used (see **4.4 Special Warnings and Precautions For Use**).

6.3 SHELF LIFE

2 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.
Store the bottle in an upright position with the cap tightly closed.
DESFLURANE must be kept in the original container until immediately prior to use.

6.5 NATURE AND CONTENTS OF CONTAINER

250 mL amber Type III glass bottle, and PVC coating on the outside of the Bottle with HDPE / EPDM closure and an aluminium crimp.

Packaged product is supplied in boxes of 6.

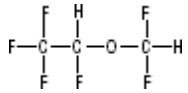
PIRAMAL DESFLURANE is only compatible with Piramal Fill Port Vaporiser.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
Accidental exposure of health professionals to desflurane can lead to a risk of undesirable effects.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure and CAS number
Active ingredient: desflurane
Molecular formula: $C_3H_2F_6O$
Molecular weight: 168.04
Chemical name: (±) 2-difluoromethyl-1,2,2,2-tetrafluoroethyl ether.
Chemical Structure:



CAS Number: 57041-67-5

Physicochemical Characteristics:
Solubility: Desflurane is not miscible with aqueous substances. It is miscible with the common organic solvents including methanol, acetone, ether, chloroform, methylene chloride, acetonitrile, and hexane in all proportions.

Physical Characteristics: Desflurane is a colourless, mobile liquid, practically odourless and tasteless at below 23°C.

Boiling Point: 22.8°C

Polymorphism: Desflurane does not exhibit polymorphism.

Specific Gravity: 1.4672g/mL (determined at 15°C)

Vapour Density: 3g/L at 1 atm (22°C)

Vapour Pressure (mm Hg): @ 20°C – 669
@ 22°C – 731
@ 23°C – 764
@ 24°C – 798
@ 26°C – 869

Minimum Flammable Concentration:
19.75% (70% N_2O/30% O_2)
17.8% (100% O_2)

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription Only Medicine

8 SPONSOR

PIRAMAL CRITICAL CARE PTY LTD
Level 20, Tower A, The Zenith,
821 Pacific Highway,
Chatswood, NSW, 2067, Australia

9 DATE OF FIRST APPROVAL

21-JAN-2020

10 DATE OF REVISION

Section Changed	Summary of new information

References:

[1] Anesthesiology 1995:83(5): 1125-1129.