PHYSICIAN'S PRESCRIBING INFORMATION

1. NAME OF THE MEDICINAL PRODUCT

Suprane

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Desflurane, supplied as pure drug substance

3. PHARMACEUTICAL FORM

Solution for inhalation

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Suprane is indicated as an inhalation agent for induction and/or maintenance of anaesthesia in adults and maintenance of anaesthesia in infants and children.

4.2 Posology and method of administration

Method of administration
Desflurane is administered by inhalation.
Desflurane should only be administered by persons trained in the administration of general anaesthesia using a vaporizer specifically designed and designated for use with desflurane.

Premedication
Premedication should be selected according to the needs of the individual patient taking into account that salivary secretions are stimulated. The use of anticholinergic drugs is a matter of choice for the anaesthetist.

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

Effects on Concomitant Therapy
Opioids or benzodiazepines decrease the amount of desflurane required to produce anaesthesia.
Desflurane decreases the required doses of neuromuscular blocking agents (see Table 2, section 4.5). If added relaxation is required, supplemental doses of muscle relaxants may be used (See section 4.5).

Dosage

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

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

Age	N*	100% Oxygen	N*	60% Nitrous Oxide/40% Oxygen
2 weeks	6	9.2 ± 0.0	-	-
10 weeks	5	9.4 ± 0.4	-	-
9 months	4	10.0 ± 0.7	5	7.5 ± 0.8
2 years	3	9.1 ± 0.6	-	-
3 years	-	-	5	6.4 ± 0.4
4 years	4	8.6 ± 0.6	-	-
7 years	5	8.1 ± 0.6	-	-
25 years	4	7.3 ± 0.0	4	4.0 ± 0.3
45 years	4	6.0 ± 0.3	6	2.8 ± 0.6
70 years	6	5.17 ± 0.6	6	1.67 ± 0.4

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

Induction of Anaesthesia in Adults

In adults, a starting concentration of 3% is recommended, increased in 0.5-1.0% increments every 2 to 3 breaths. Inspired concentrations of 4-11% of desflurane usually produce surgical anaesthesia in 2-4 minutes. Higher concentrations up to 15% may be used. Such concentrations of desflurane will proportionately dilute the concentration of oxygen and commencing administration of oxygen should be 30% or above. 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.

Desflurane should be administered at 0.8 MAC or less, and in conjunction with a barbiturate induction and hyperventilation (hypocapnia) until cerebral decompression in patients with known or suspected increases in CSFP. Appropriate attention must be paid to maintain cerebral perfusion pressure (See section 4.4).

During induction in adults, the overall incidence of oxyhemoglobin desaturation (SpO_2 < 90%) was 6%. High concentrations of desflurane may induce upper airway adverse events. (See section 4.8).

Induction of Anaesthesia in Children

Desflurane is not indicated for use as an inhalation induction agent in children and infants because of the frequent occurrence of cough, breath holding, apnoea, laryngospasm and increased secretions (see section 4.4).

Maintenance of Anaesthesia in Adults

Surgical levels of anaesthesia may be sustained with 2-6% concentration of desflurane when nitrous oxide is used concomitantly. Desflurane at 2.5-8.5 % may be required

when administered using oxygen or oxygen enriched air. In adults, surgical levels of anaesthesia may be sustained at a reduced concentration of desflurane when nitrous oxide is used concomitantly.

Maintenance of Anaesthesia in Children
Desflurane is indicated for maintenance of anaesthesia in infants and children. Surgical levels of anaesthesia may be maintained in children with end-tidal concentrations of 5.2 to 10% desflurane with or without the concomitant use of nitrous oxide. Although endtidal concentrations of up to 18% desflurane have been administered for short periods of time, if high concentrations are used with nitrous oxide it is important to ensure that the inspired mixture contains a minimum of 25% oxygen.

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

Blood Pressure and Heart Rate During Maintenance
Blood pressure and heart rate should be monitored carefully during maintenance as part of the evaluation of depth of anaesthesia (See section 4.4).

Dosage in Renal and Hepatic Impairment
Concentrations of 1-4% desflurane in nitrous oxide/oxygen have been used successfully 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 is contraindicated in patients:

- with hypersensitivity to the active substance.
- in whom general anaesthesia is contraindicated.
- with a known sensitivity to halogenated agents.
- with a known or suspected genetic susceptibility to malignant hyperthermia.
- with a history of confirmed hepatitis due to a halogenated inhalational anaesthetic or with a history of unexplained moderate to severe hepatic dysfunction (e.g. jaundice associated with fever and/or eosinophilia) after anaesthesia with a halogenated inhalational anaesthetic.

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

Desflurane is contraindicated when used as sole agent for anaesthetic induction in patients at risk of coronary artery disease or in patients where increases in heart rate or blood pressure are undesirable (see section 4.4).

4.4 Special warnings and precautions for use

Desflurane should only be administered by persons trained in the administration of general anaesthesia using a vaporizer 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.

Warnings:

Malignant Hyperthermia (MH)
In susceptible individuals, potent inhalation anaesthetic agents may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. Desflurane was shown to be a potential trigger of malignant hyperthermia. The clinical syndrome is signaled by hypercapnia, and may include muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and/or unstable blood pressure. Some of these non-specific signs may also appear during light anaesthesia: acute hypoxia, hypercapnia, and hypovolemia. Treatment of malignant hyperthermia includes discontinuation of triggering agents, administration of intravenous dantrolene sodium, and application of supportive therapy. Renal failure may appear later, and urine flow should be monitored and sustained if possible. Desflurane should not be used in subjects known to be susceptible to MH. Fatal outcome of malignant hyperthermia has been reported with desflurane.

Perioperative Hyperkalemia
Use of inhaled anaesthetic agents, has been associated with very rare increases in serum potassium levels that have resulted in cardiac arrhythmias, and death in children during the postoperative period. The condition has been described in patients with latent as well as overt neuromuscular disease, particularly Duchenne muscular dystrophy. Use of suxamethonium has been associated with most, but not all, of these cases. These patients showed evidence of muscle damage with increased serum creatinine kinase concentration and myoglobinuria. Despite the similarity in presentation to malignant hyperthermia, none of these patients exhibited signs or symptoms of muscle rigidity or hypermetabolic state.

Prompt and vigorous treatment for hyperkalaemia and arrhythmias is recommended. Subsequent evaluation for latent neuromuscular disease is indicated.

Paediatric Inhalation Induction
Desflurane is not indicated for use as an inhalation induction agent in children and infants because of the frequent occurrence of cough, breath holding, apnoea, laryngospasm and increased secretions.

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

Maintenance of Anaesthesia in Children
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) or face mask in children 6 years old or younger because of the increased potential for adverse respiratory events, e.g. coughing and laryngospasm, especially with removal of the LMA under deep anaesthesia.

Obstetrics
Due to the limited number of patients studied, the safety of desflurane has not been established for use in obstetric procedures. Desflurane is a uterine-relaxant and reduces the uterine-placental blood-flow (See section 4.6).

Isolated reports of QT prolongation, very rarely associated with torsade de points (in exceptional cases, fatal), have been received (see section 4.8). Caution should be exercised when administering desflurane to susceptible patients (e.g. patients with congenital or acquired Long QT Syndrome, hypokalamia, congestive heart failure or patients taking drugs that can prolong with QT interval).

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

Desflurane, as other volatile anaesthetics, may produce a dose-dependent increase in cerebrospinal fluid pressure (CSFP) when administered to patients with space occupying lesions. In such patients, desflurane should be administered at 0.8 MAC or less, and in conjunction with a barbiturate induction and hyperventilation (hypocapnia) until cerebral decompression in patients with known or suspected increases in CSFP. Appropriate attention must be paid to maintain cerebral perfusion pressure.

In patients with coronary artery diseases, 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 agent for anaesthetic induction in patients at risk of coronary artery disease or in patients where increases in the heart rate or blood pressure are undesirable. It should be used with other medications, preferably intravenous opioids and hypnotics.

During maintenance of anaesthesia, increases in heart rate and blood pressure occurring after rapid incremental increases in end-tidal concentration of 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.

Hypotension and respiratory depression increase as anaesthesia is deepened.

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.

Desflurane, like some other inhalation anaesthetics, can react with desiccated carbon dioxide (CO_2) absorbents to produce carbon monoxide that may result in elevated levels of carboxyhemoglobin in some patients. Case reports suggest that barium hydroxide lime and soda lime become desiccated when fresh gases are passed through the CO_2 canister at high flow rates over many hours or days. When a clinician suspects that CO_2 absorbent may be desiccated, it should be replaced before the administration of desflurane.

As with other rapid-acting anesthetic 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. Emergence from anaesthesia in children may evoke a brief state of agitation that may hinder cooperation.

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

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

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

4.5 Interaction with other medicinal products and other forms of interaction

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

Non-depolarizing and depolarizing muscle relaxants
Commonly used muscle relaxants are potentiated by desflurane.
Anaesthetic concentrations of desflurane at equilibrium reduce the ED_{95} of suxamethonium 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 (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	*NA	*NA
1.25 MAC/ 60% N_2O/O_2	0.018	0.119	*NA	*NA
1.25 MAC/O_2 100% O_2	0.022	0.120	0.362	0.019

*NA = not available

Pre-anaesthetic Drugs

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

Sedatives

Patients anaesthetised with different concentrations of desflurane who received increasing doses of fentanyl 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 (%)	%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

4.6 Fertility, pregnancy and lactation

Due to the limited number of patients studied, the safety of desflurane has not been established for use in obstetric procedures. Desflurane is a uterine relaxant and reduces the uterine-placental blood-flow. Studies in animals have shown reproductive toxicity. (see section 5.3).

There are no adequate data from the use of desflurane in pregnant or lactating women, therefore desflurane is not indicated for use during pregnancy and lactation.

4.7 Effects on ability to drive and use machines

There is no information on 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 Undesirable effects

As with all potent inhaled anaesthetics desflurane may cause dose-dependent cardio-respiratory depression. Most other adverse events are mild and transient. 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.

ADR frequency is based upon the following scale: Very Common (≥ 1/10); Common (≥ 1/100 - <1/10), Uncommon (≥ 1/1,000 - <1/100), Rare (≥ 1/10,000 - <1/1,000), Very Rare (< 1/10,000), Unknown (adverse reactions reported in the post-marketing experience).

Adverse Reactions		
System Organ Class (SOC)	**Preferred MedDRA Term**	**Frequency**
INFECTIONS AND INFESTATIONS	Pharyngitis	Common
BLOOD AND THE LYMPHATIC SYSTEM DISORDERS	Coagulopathy	Unknown
METABOLISM AND NUTRITION DISORDERS	Hyperkalemia Hypokalemia Metabolic acidosis	Unknown Unknown Unknown
PSYCHIATRIC DISORDERS	Breath holding^{+} Agitation Delirium	Common Uncommon Unknown
NERVOUS SYSTEM DISORDERS	Headache Dizziness Convulsions	Common Uncommon Unknown
EYE DISORDERS	Conjunctivitis Ocular icterus	Common Unknown
CARDIAC DISORDERS	Nodal arrhythmia Bradycardia Tachycardia Hypertension Myocardial infarction Myocardial ischemia Arrythmia Cardiac arrest Torsade de pointes Ventricular failure Ventricular hypokinesia Electrocardiogram QT prolonged	Common Common Common Common Uncommon Uncommon Uncommon Unknown Unknown Unknown Unknown Unknown
VASCULAR DISORDERS	Vasodilation Malignant hypertension Hemorrhage Hypotension Shock	Uncommon Unknown Unknown Unknown Unknown
RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS	Apnea^{+} Cough^{+} Laryngospasm***** Hypoxia^{+} Respiratory arrest Respiratory failure Respiratory distress Bronchospasm Hemoptysis	Common Common Common Uncommon Unknown Unknown Unknown Unknown Unknown

Adverse Reactions		
System Organ Class (SOC)	**Preferred MedDRA Term**	**Frequency**
GASTROINTESTINAL DISORDERS	Vomiting[+] Nausea[+] Salivary hypersecretion[+] Pancreatitis acute Abdominal pain	Very Common Very Common Common Unknown Unknown
HEPATOBILIARY DISORDERS	Hepatic failure Hepatic necrosis Hepatitis Cytolytic hepatitis Cholestasis Jaundice Hepatic function abnormal Liver disorder	Unknown Unknown Unknown Unknown Unknown Unknown Unknown Unknown
SKIN AND SUBCUTANEOUS TISSUE DISORDER	Urticaria Erythema	Unknown Unknown
MUSCULOSKELETAL, CONNECTIVE TISSUE AND BONE DISORDERS	Myalgia Rhabdomyolysis	Uncommon Unknown
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Hyperthermia malignant Asthenia Malaise	Unknown Unknown Unknown
INVESTIGATIONS	Increased creatinine phosphokinase ECG abnormal Electrocardiogram ST-T change Electrocardiogram T wave inversion Transaminases (alanine and aspartate aminotransferase) increased Blood bilirubin increased Coagulation test abnormal Ammonia increased	Common Common Unknown Unknown Unknown Unknown Unknown Unknown

Adverse Reactions		
System Organ Class (SOC)	**Preferred MedDRA Term**	**Frequency**
INJURY, POISONING, AND PROCEDURAL COMPLICATIONS	Agitation postoperative	Unknown
	Dizziness§	Unknown
	Migraine§	Unknown
	Tachyarrhythmia§	Unknown
	Palpitations§	Unknown
	Eye burns§	Unknown
	Blindness transient§	Unknown
	Encephalopathy§	Unknown
	Ulcerative keratitis§	Unknown
	Ocular hyperemia§	Unknown
	Visual acuity reduced§	Unknown
	Eye irritation§	Unknown
	Eye pain§	Unknown
	Fatigue§	Unknown
	Skin burning sensation§	Unknown
	Drug administration error§	Unknown

* reported during induction with desflurane

+ reported during induction and maintenance with desflurane

§ Reactions due to accidental exposures to non-patients

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form in the link: http://sideeffects.health.gov.il

4.9 Overdose

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 hypotension in ventilated patients in whom hypercarbia 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. Support and maintain adequate haemodynamics.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Desflurane is one of a family of halogenated methylethylethers which are administered by inhalation producing a dose-related, reversible loss of consciousness and of pain sensations, suppression of voluntary motor activity, reduction of autonomic reflexes and sedation of respiration and the cardiovascular system.
Other members of the series include enflurane and its structural isomer isoflurane which are halogenated with chlorine as well as fluorine. Desflurane is halogenated exclusively with fluorine. As suggested by its structure, the low blood/gas partition coefficient of desflurane (0.42) is lower than that of other potent inhaled anaesthetics such as isoflurane (1.4) and even lower than that of nitrous oxide (0.46). These data indicate that desflurane would meet the need for an agent characterised by rapid recovery and that it is particularly suited for use in outpatient anaesthesia where this is an important property.
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 on 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.

5.2 Pharmacokinetic properties

a. General Characteristics

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

b. Characteristics in patients

The pharmacological effect is proportional to the inspired concentration of desflurane. The main adverse effects are extensions of the pharmacological action.
MAC decreases with increasing age. A reduction of dosage is recommended in hypovolaemic, hypotensive and debilitated patients, as discussed under Warnings above.

5.3 Preclinical safety data

In swine, desflurane does not sensitize the myocardium to exogenously administered epinephrine (adrenaline). 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.

Published studies in animals (including primates) at doses resulting in light to moderate anaesthesia demonstrate that the use of anaesthetic agents during the period of rapid brain growth or synaptogenesis results in cell loss in the developing brain that can be associated with prolonged cognitive deficiencies. The clinical significance of these nonclinical findings is not known.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Not applicable.

6.2 Incompatibilities

None.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

6.4 Special precautions for storage

Store below 30°C.
Store in an upright position with cap firmly in place.

6.5 Nature and contents of container

Suprane is presented in 310 ml aluminium bottles that are lined with an internal epoxyphenolic resin protective lacquer, containing 240 ml of desflurane. The bottles are closed with an integrated crimped-on valve closure with stainless steel, nylon, ethylene-propylene copolymer (EPDM) and polyethylene product contact components. The crimped-on valve closure is directly compatible with the filling port of the desflurane vaporiser.

6.6 Instructions for use/handling

Replace cap after use.

Desflurane should only be administered by persons trained in the administration of anaesthesia, using a vaporizer specifically designed and designated for use with desflurane.

7. REGISTRATION NUMBER:

101 32 28466 00

8. MANUFACTURER

Baxter Healthcare Corporation, USA
One Baxter Parkway, Deerfield. IL 60015, USA

9. REGISTRATION HOLDER

Baxter Healthcare Distribution Ltd.
34 Jerusalem St., Ra'anana 4350110

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