1. NAME OF THE MEDICINAL PRODUCT
Desolox Liquid for Inhalation, 100% v/v

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Desflurane 100% (v/v)

3. PHARMACEUTICAL FORM
Inhalation vapour liquid.
Clear, colourless, liquid.

4. Clinical particulars
4.1 Therapeutic indications
Desolox (Desflurane) is indicated as an inhalation agent for induction and/or maintenance of anaesthesia for inpatient and outpatient in adults and maintenance of anaesthesia in infants and children.

4.2 Posology and method of administration
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	5.2±0.6	6	1.7

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

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

Premedication
Issues such as whether or not to premedicate and the choice of premedicant(s) must be

individualised. Patients scheduled to be anaesthetised with desflurane frequently received IV pre-anaesthetic medication, such as opioids and/or benzodiazepines

Induction of Anaesthesia in Adults

In adults, a starting concentration of 3% is recommended, increased in 0.5-1.0% increments every 2 to 3 breaths. Inspired concentrations of 4-11% Desflurane produce surgical anaesthesia within 2 to 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. During induction in adults, the overall incidence of oxyhaemoglobin desaturation (SpO_2 < 90%) was 6%. High concentrations of Desflurane may induce upper airway adverse events. (See section Undesirable effects). 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 oxygen or nitrous oxide/oxygen.
Desflurane should be administered at 0.8 MAC or less, and in conjunction with a barbiturate induction and hyperventilation (hypocapnia) until cerebral decompression in patients with known or suspected increases in cerebrospinal fluid pressure (CSFP). Appropriate attention must be paid to maintain cerebral perfusion pressure. (See section Special Warnings and Precautions for Use.)

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, apnea, laryngospasm and increase in secretions.

Maintenance of Anaesthesia in Adults

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

Blood Pressure and Heart Rate During Maintenance

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

Dosage in Renal and Hepatic Impairment

Concentrations of 1-4% 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.

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

Opioids or benzodiazepines decrease the amounts of Desflurane required to produce anaesthesia. Desflurane decreases the required doses of neuromuscular blocking agents. If added relaxation is required, supplemental doses of muscle relaxants may be used.

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

4.3 Contraindications

Desflurane is contraindicated in patients:

- in whom general anesthesia 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 anesthetic or with a history of unexplained moderate to severe hepatic dysfunction (e.g., jaundice associated with fever and/or eosinophilia) after anesthesia with a halogenated inhalation anesthetic.
- 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.

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 beimmediately 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 individuals 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 Fertility, pregnancy and lactation). Isolated reports of QT prolongation, very rarely associated with torsade de pointes (in exceptional cases, fatal), have been received. Caution should be exercised when administering desflurane to susceptible patients e.g. patients with existing QTc prolongation.

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 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 agent for anesthetic induction in patients at risk of coronary artery disease or in patients where increases in heart rate or blood pressure are undesirable. It should be used with other medications, preferably intravenous opioids and hypnotics.
During maintenance of anaesthesia, increases in heart rate and blood pressure occurring after rapid incremental increases in end-tidal concentration of 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.

<u>Glucose elevation</u>
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	0.123	*NA	*NA
1.25 MAC/60% N_2O/O_2	0.018	0.091	*NA	*NA
1.25 MAC/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. 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

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.

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, Common, Uncommon, Rare, Very Rare, 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**	Unknown
	Hypokalemia	Unknown
	Metabolic acidosis	Unknown
PSYCHIATRIC DISORDERS	**Breath holding**[+]	Common
	Agitation	Uncommon
NERVOUS SYSTEM DISORDERS	**Headache**	Common
	Dizziness	Uncommon
	Convulsions	Unknown
EYE DISORDERS	**Conjunctivitis**	Common
	Ocular icterus	Unknown
CARDIAC DISORDERS	**Nodal arrhythmia**	Common
	Bradycardia	Common
	Tachycardia	Common
	Hypertension	Common
	Myocardial infarction	Uncommon
	Myocardial ischemia	Uncommon
	Arrhythmia	Uncommon
	Cardiac arrest	Unknown

Adverse Reactions		
System Organ Class (SOC)	**Preferred MedDRA Term**	**Frequency**
	Torsade de pointes	Unknown
	Ventricular failure	Unknown
	Ventricular hypokinesia	Unknown
	Artial fibrilation	Unknown
VASCULAR DISORDERS	**Vasodilation**	Uncommon
	Malignant hypertension	Unknown
	Hemorrhage	Unknown
	Hypotension	Unknown
	Shock	Unknown
RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS	**Apnea**[+]	Common
	Cough[+]	Common
	Laryngospasm[*]	Common
	Hypoxia[+]	Uncommon
	Respiratory arrest	Unknown
	Respiratory failure	Unknown
	Respiratory distress	Unknown
	Bronchospasm	Unknown
	Hemoptysis	Unknown
GASTROINTESTINAL DISORDERS	**Vomiting**[+]	Very Common
	Nausea[+]	Very Common
	Salivary hypersecretion[+]	Common
	Pancreatitis acute	Unknown
	Abdominal pain	Unknown
HEPATOBILIARY DISORDERS	**Hepatic failure**	Unknown
	Hepatic necrosis	Unknown
	Hepatitis	Unknown
	Cytolytic hepatitis	Unknown
	Cholestasis	Unknown
	Jaundice	Unknown
	Hepatic function abnormal	Unknown
	Liver disorder	Unknown
SKIN AND SUBCUTANEOUS TISSUE DISORDER	**Urticaria**	Unknown
	Erythema	Unknown
MUSCULOSKELETAL, CONNECTIVE TISSUE AND BONE DISORDERS	**Myalgia**	Uncommon
	Rhabdomyolysis	Unknown
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**Hyperthermia malignant**	Unknown
	Asthenia	Unknown
	Malaise	Unknown
INVESTIGATIONS	**Increased creatinine phosphokinase**	Common
	ECG abnormal	Common
	Electrocardiogram ST-T change	Unknown
	Electrocardiogram T wave inversion	Unknown
	Alanine aminotransferase increased	Unknown
	Aspartate aminotransferase increased	Unknown
	Blood bilirubin increased	Unknown

Adverse Reactions		
System Organ Class (SOC)	**Preferred MedDRA Term**	**Frequency**
	Coagulation test abnormal	Unknown
	Ammonia increased	Unknown
INJURY, POISONING, AND PROCEDURAL COMPLICATIONS§	**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

* Reported during induction with desflurane
+ reported during induction and maintenance with desflurane
§ All of reactions categorized within this SOC were accidental exposures to non-patients

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.
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.

5.2 Pharmacokinetic properties

a. General Characteristics

As predicted from its physicochemical profile, 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.

6. Pharmaceutical particulars

6.1 List of excipients

Not applicable.

6.2 Incompatibilities

None.

6.3 Shelf life

Please refer to the expiry date on the product labels.

6.4 Special precautions for storage

Store below 30°C.

Store in an upright position with cap firmly in place. Once open, use within 7 days and store at 25ºC. Replace cap after each use.

6.5 Nature and contents of container

250-mL amber-colored plastic-coated glass bottles containing 240mL of desflurane, sealed with a semi- transparent valve assembly and aluminum ferrule, and secured with PET sealing film.

6.6 Special precautions and instructions for use, handling and disposal

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.

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

Principle routes of exposure include:

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

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

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

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

7. Manufacturer

Manufactured by:
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