DESFLO

1. PRODUCT NAME

Desflo (Desflurane, USP, Liquid for Inhalation)

2. NAME AND STRENGTH OF ACTIVE INGREDIENT(S)

Desflurane 100% (v/v), (INN: Desflurane)

3. PRODUCT DESCRIPTION

Clear, colorless, liquid.

4. PHARMACODYNAMICS

Desflurane is one of a family of halogenated methyl ethyl ethers, which are administered by inhalation, producing a dose-related temporary loss of consciousness and of pain sensations, suppression of voluntary motor activity, reduction of autonomic reflexes, and depression of respiration and the cardiovascular system.

Other members of the series include enflurane and isoflurane which are halogenated with chlorine as well as fluorine. Desflurane is halogenated exclusively with fluorine.

As suggested by its structure, the diffusion coefficient of gas in the blood for desflurane (0.42) is lower than all available volatile anesthetics (isoflurane has 1.4 blood-gas partition coefficient), and slightly lower than nitrous oxide (0.46). These data indicate that desflurane would meet the need for an agent characterised by rapid recovery.

Animal studies have shown more rapid induction and awakening with desflurane than from isoflurane anesthesia, with similar cardiovascular profile. EEG monitoring did not detect epileptogenic or other central nervous system undesirable effects during the desflurane-anesthesia, and concomitant use of adjuvant medicinal products produced no unanticipated or toxic EEG responses.

Studies in pigs susceptible to malignant hyperthermia indicated that desflurane is a powerful trigger for malignant hyperthermia.

Pharmacological effect of desflurane correlates with end-tidal desflurane concentration.

PHARMACOKINETICS

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 anesthetics, and allows faster induction. It also washes out of the body more rapidly allowing quick recovery and

flexibility in adjustment of the depth of anesthesia. Desflurane is eliminated via the lungs, undergoing only minimal metabolism (0.02%), hence low potential for toxicity.

The MAC (minimum alveolar concentration) decreases with increasing age. A reduction of dose is recommended in hypovolemic, hypotensive and weak patients.

5. INDICATION

Desflurane is indicated as an inhalation agent for induction and/or maintenance of anaesthesia for inpatient and outpatient surgery in adults and maintenance of anaesthesia for inpatient and outpatient paediatric surgery.
Desflurane is not indicated for use as an inhalation induction agent in children and infants

6. RECOMMENDED DOSE

Desflurane should be administered by persons trained in the administration of general anesthesia using a vaporizer specifically designed and calibrated for use with desflurane.

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

The administration of general anesthesia must be individualized based on the patient's response. It is determined depending on the desired effect, taking into consideration of the patient's age and his clinical status.

MAC-values (minimum alveolar concentration at which 50% of patients show no response to a standardized surgical incision) for desflurane decrease with increasing patient age. The dose of desflurane should be adjusted accordingly.

The percentage concentration of desflurane corresponding to 1 MAC has been determined within carrier gas as listed in Table 1 below.

Table 1 - Percentage concentration of desflurane corresponding to 1 MAC according to patient age and inhalation mixture (Mean ± SD)

Age	N*	100 % Oxygen	N*	60% Nitrous Oxide/ 40% Oxygen
2 weeks	6	9.2 ± 0.0	-	-
10 weeks	5	9.4 ± 0.4	-	-
9 months	4	10.0 ± 0.7	5	7.5 ± 0.8
2 years	3	9.1 ± 0.6	-	-
3 years	-	-	5	6.4 ± 0.4
4 years	4	8.6 ± 0.6	-	-
7 years	5	8.1 ± 0.6	-	-
25 years	4	7.3 ± 0.0	4	4.0 ± 0.3
45 years	4	6.0 ± 0.3	6	2.8 ± 0.6
70 years	6	5.2 ± 0.6	6	1.7 ± 0.4

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

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 cerebrospinal fluid pressure (CSFP). Appropriate attention must be paid to maintain cerebral perfusion pressure.

Maintenance of Anesthesia in adults
Desflurane is indicated for maintenance of anesthesia in intubated adults. Surgical levels of anesthesia 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 anesthesia may be sustained at a reduced concentration of desflurane when nitrous oxide is used concomitantly.

Maintenance of Anesthesia in children
Desflurane is indicated for maintenance of anesthesia in intubated infants and children. Surgical levels of anesthesia 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.

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.

Concomitant Therapy
Desflurane can be combined with other substances commonly used in anesthesia, preferably intravenous opioids benzodiazepines and hypnotics. Opioids or benzodiazepines decrease the amount of desflurane required to produce anesthesia.

The need of Desflurane also decreases with the concomitant use of nitrous oxide (N2O).

Desflurane decreases the required doses of neuromuscular blocking agents. If added relaxation is required, supplemental doses of muscle relaxants may be used.

Patients with Renal and Hepatic Impairment
Concentrations of 1-4% desflurane together with nitrous oxide or oxygen have been administered successfully in patients with chronic renal or hepatic impairment and during renal transplantation surgery. Because of low metabolism, dose adjustment in patients with renal and hepatic impairment is not necessary.

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 anesthesia.

7. MODE OF ADMINISTRATION

Desflurane is administered by inhalation.

8. CONTRAINDICATION

- Desflurane should not be used for patients in whom general anesthesia is contraindicated.

- In patients with hypersensitivity to halogenated anesthetics.

- In patients with known or suspected propensity to malignant hyperthermia (MH) or with a corresponding hereditary disposition to MH.

- Desflurane should not be used in patients in whom liver dysfunction, unexplained fever or leukocytosis has occurred after a previous halogenated anesthetic administration.

- Desflurane is contraindicated for use as an inhalation induction agent in paediatric patients.

9. WARNINGS AND PRECAUTIONS

Malignant Hyperthermia (MH)
In susceptible individuals (history of malignant hyperthermia, myopathies such as muscular dystrophies, king syndrome, myotinic dystrophy, central core myopathy), potent inhalation anesthetics 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 anesthesia: acute hypoxia, hypercapnia, and hypovolemia. Treatment of malignant hyperthermia includes discontinuation of triggering medicinal products, 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.

Perioperative Hyperkalemia
Use of inhaled anesthetics, 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 hyperkalemia and arrhythmias is recommended. Subsequent evaluation for latent neuromuscular disease is indicated.

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 utero-placental blood flow.

Glucose elevation
Desflurane has been associated with some elevation of glucose intra-operatively.

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

Desflurane 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. Appropriate attention must be paid to maintain cerebral perfusion pressure.

During maintenance of anesthesia, increases in heart rate and blood pressure occurring after rapid incremental increases in end-tidal concentration of desflurane may not represent inadequate anesthesia. The changes due to sympathetic activation resolve in approximately 4 minutes. Increases in heart rate and blood pressure occurring before or in the absence of a rapid increase in desflurane concentration may be interpreted as light anesthesia.

Hypotension and respiratory depression increase as anesthesia is deepened.

Desflurane 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. The formation of CO is not clinically significant when the adsorbent is normally hydrated. Comply strictly with the instructions of use of CO_2 adsorbents given by the manufacturer. When a clinician suspects that CO_2 absorbent may be desiccated, it should be replaced before the administration of desflurane.

Rapid emergence with desflurane should be taken into account in cases where post- anesthesia 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- anesthesia care unit stay.

Repeated anesthesia within a short period of time should be approached with caution.

The effects of desflurane in patients with hypovolemia, hypotension or poor general condition have not been widely investigated. In these patients, it is advisable to reduce the concentrations.

Desflurane should not be given to patients that are prone to bronchoconstriction, due to the risk of bronchospasms.

Desflurane has coronary dilating effect. In patients with coronary heart disease, it is important to maintain an unobstructed hemodynamics to prevent myocardial ischemia. Desflurane should not be used as the sole means of anesthesia in patients at risk of a coronary heart disease, increased heart rate or increased blood pressure.

Middle ear surgeries
Desflurane, as well as other volatile anesthetics increase middle ear pressure especially in children, and hence it is recommended that middle ear pressure be monitored during anesthesia with desflurane.

Pediatric population
Desflurane should NOT be used for maintenance anesthesia with LMA.

Desflurane should be used with caution in children with a recent infection of the upper airways since there might be a risk of bronchoconstriction and an increased airway resistance.

Effects on ability to drive and use machines
There are no data on the effects of desflurane following anesthesia on the ability to drive or use machines. However, patients should be advised that the ability to perform such tasks may be impaired after general anesthesia. It is therefore advisable to avoid such tasks for a period of 24 hours after anesthesia.

10. INTERACTIONS WITH OTHER MEDICAMENTS

Desflurane potentiates the action of myorelaxants commonly used. Nitrous oxide used simultaneously decreases the MAC of desflurane (see Table 1).

Depolarizing and nondepolarizing Myorelaxants
Commonly used muscle relaxants are potentiated by desflurane. Anesthetic concentrations of desflurane at equilibrium reduce the ED95 of suxamethonium by approximately 30% and that of atracurium and pancuronium by approximately 50% compared to N2O/opioid anesthesia

Table 2 shows the doses of pancuronium, atracurium and suxamethonium required to obtain a 95% depression (ED95) of neuromuscular transmission according to different concentrations of desflurane (these doses are identical to those required for isoflurane). The ED95 of vecuronium is lower than 14%, with desflurane than isoflurane. In addition, recovery from neuromuscular blockade is longer with desflurane than isoflurane.

Table 2 - Determination (mg / kg) of myorelaxant inducing a 95% depression of neuromuscular transmission.

MAC Desflurane	Pancuronium	Atracurium	Suxamethonium	Vecuronium
0.65. MAC/60% N_2O/O_2	0.026	0.123	* ND	* ND
1.25. MAC /60% N_2O/O_2	0.018	0.091	* ND	* ND
1.25. MAC /100% O_2	0.022	0.120	0.362	0.019

* ND = not determined

Pre-anesthetic medication

No clinically significant of adverse interactions related to the widespread use of pre- anesthetic medicinal products or medicinal products used during anesthesia (intravenous anesthetics and local anesthetics) have been reported during clinical trials. The effect of desflurane on the availability of other medicinal products has not been determined.

Opiates and benzodiazepines

Patients anesthetized with different concentrations of desflurane and receiving increasing doses of fentanyl showed a significant reduction in anesthetic requirements or MAC. The administration of increasing doses of midazolam intravenously shows a small decrease in MAC (see Table 3). It is anticipated that there will be a similar influence on MAC with other opioid and sedative medicinal products.

Table 3 - Effect of Fentanyl or Midazolam on Desflurane concentration corresponding to 0.6-0.8 MAC/O_2

	Concentration* (%) of desflurane in O_2	% Reduction in Concentration
No Fentanyl	6.33- 6.35	-
Fentanyl (3 µg/kg)	3.12-3.46	46-51
Fentanyl (6 µg/kg)	2.25 -2.97	53-64
No midazolam	5.85- 6.86	-
Midazolam (25 µg/kg)	4.93	15.7
Midazolam (50 µg/kg)	4.88	16.6

* Patients aged 18-65 years

11. PREGNANCY AND LACTATION

Pregnancy
There are no adequate and well-controlled studies in pregnant women. Desflurane is a uterine relaxant and reduces the uterine-placental blood flow. Limited animal data do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, Desflurane should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Breast-feeding
It is unknown whether desflurane is excreted in human milk. The potential risk for the nursing infant is unknown. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Desflurane therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

12. UNDESIRABLE EFFECTS

Desflurane may cause dose-dependent cardiac and respiratory depression and a slight intraoperative increase in blood glucose levels. Most undesirable effects are mild to moderate. Nausea and vomiting have been observed in the postoperative period, common sequelae of surgery and general anesthesia, which may be due to inhalational anesthetic, other medicinal products administered intraoperatively or post-operatively and to the patient's response to the surgical procedure.

The adverse reactions listed below are categorized using the following frequency convention:

Very common (≥ 1 / 10)
Common (≥ 1 / 100 to < 1 / 10)
Uncommon (≥ 1 / 1000 to < 1 / 100)
Rare (≥ 1/ 10 000 to < 1 / 1000)
Very rare (<1 / 10 000)
Not known (frequency cannot be estimated from the available data)

Table 4 - Adverse Drug Reactions

System Organ Class	Side Effect	Frequency
Infections and infestations	Pharyngitis	Common
Blood and lymphatic system disorders	Coagulopathy	Not known
Metabolism and nutrition disorders	Hyperkalemia Hypokalemia Metabolic acidosis	Not known Not known Not known
Psychiatric disorders	Breath Holding Agitation	Common Uncommon
Nervous system disorders	Headache Drowsiness Convulsions	Common Uncommon Not known

Eye disorders	Conjuctivitis Ocular Icterus	Common Not known
Cardiac disorders	Nodal arrhythmia Bradycardia Tachycardia Hypertension Myocardial infarction Myocardial ischaemia Arrhythmia Cardiac arrest Torsades de Pointes Ventricular failure Ventricular hypokinesia	Common Common Common Common Uncommon Uncommon Uncommon Not known Not known Not known Not known
Vascular disorders	Vasodilation Malignant hypertension Hemorrhage Hypotension Shock	Uncommon Not known Not known Not known Not known
Respiratory, thoracic and mediastinal disorders	Apnea[1] Cough[1] Hypoxia[1] Respiratory failure Difficulty in breathing Bronchospasm Hemoptysis	Common Common Uncommon Not known Not known Not known Not known
Gastrointestinal disorders	Vomiting[1] Nausea[1] Excessive saliva secretion[1] Acute pancreatitis Abdominal pain	Very common Very common Common Not known Not known
Hepatobiliary disorders	Liver failure Liver cell necrosis Cytolytic hepatitis Cholestasis Jaundice Impaired liver function, liver disease	Not known
Skin and subcutaneous tissue disorders	Urticaria Erythema	Not known
Musculoskeletal and connective tissue disorders	Myalgia Rhabdomyolysis	Uncommon Not known
General disorders and administration site conditions	Malignant Hyperthermia Asthenia Discomfort	Not known

Investigations	Increasing creatinine Phosphokinase Abnormal ECG Changes in the ST-T-track Inversion of the T wave in the ECG Alanine aminotransferase increased Aspartate aminotransferase increased Abnormal coagulation values Elevated ammonia levels Bilirubin increased	Common Common Not known Not known Not known Not known Not known Not known Not known
Injury, poisoning and procedural complications[2]	Dizziness Migraine Tachyarrhythmia Palpitation Burning eyes Temporary blindness Encephalopathy Ulcerative keratitis Ocular hyperaemia Decreased visual acuity Eye irritation Eye pain Fatigue Burning sensation on the skin	Not known

[1] Reported during induction and maintenance of anesthesia
[2] Reported by non-patients after accidental exposure

13. OVERDOSE AND TREATMENT

The symptoms of overdose of desflurane are anticipated to be similar to those of other volatile agents with a deepening of anesthesia, 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 overdose, the following actions should be taken: Desflurane should be stopped, a clear airway should be established and assisted or controlled ventilation with pure oxygen should be initiated. The hemodynamic function must be properly supported and maintained.

14. STORAGE CONDITION

Store below 30^{o}C.

15. DOSAGE FORMS AND PACKAGING AVAILABLE

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.

16. NAME AND ADDRESS OF MANUFACTURER

Shanghai Hengrui Pharmaceutical Co., Ltd.
No. 279, Wenjing Road, Minhang District, Shanghai, China

17. NAME AND ADDRESS OF MARKETING AUTHORIZATION HOLDER

Brandt Biotech Company Ltd.
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