Suprane (desflurane)

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

English master

Proposed version – September 2022

Clean version

1. NAME OF THE MEDICINAL PRODUCT

Suprane 100% inhalation vapour, liquid

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Desflurane 100% (v/v). One bottle contains 240 ml of desflurane.

3. PHARMACEUTICAL FORM

Inhalation vapour, liquid

Clear, colorless, liquid

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Desflurane is indicated as an inhalation agent for maintenance of general anaesthesia for inpatient and outpatient surgery in adults, adolescents and intubated infants and children.

4.2 Posology and method of administration

Posology
The administration of general anaesthesia must be individualised based on the patient's response.

Desflurane is only indicated for maintenance, and not for induction of anaesthesia (see section 4.3 and 4.4).

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

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

Age	100% oxygen	60% N_2O / 40% O_2
2 weeks	9,2±0,0	-
10 weeks	9,4±0,4	-
9 months	10,0±0,7	7,5±0,8
2 years	9,1±0,6	-
3 years	-	6,4±0,4
4 years	8,6±0,6	-
7 years	8,1±0,6	-
25 years	7,3±0,0	4,0±0,3
45 years	6,0±0,3	2,8±0,6
70 years	5,2±0,6	1,7

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.

Concomitant therapy
Desflurane can be combined with other substances commonly used in anaesthesia including sedatives, opioids, muscle relaxants and other gases. See section 4.5 for dose adjustments.

Special populations

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.

Paediatric population

Maintenance of anaesthesia in children and adolescents
Surgical levels of anaesthesia may be maintained in children and adolescents 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.

Elderly population

Maintenance of anaesthesia in elderly patients
Desflurane at 5.5-7.4% may be required when administered using oxygen or oxygen enriched air. In elder patients, surgical levels of anaesthesia may be sustained at a reduced concentration of desflurane when nitrous oxide is used concomitantly.

Method of Administration
Desflurane is administered by inhalation.

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

All patients anaesthetised with desflurane should be constantly monitored, including electrocardiogram (ECG), blood pressure (BP), oxygen saturation and end tidal carbon dioxide (CO_2.) The concentration of desflurane being delivered from a vaporizer must be known exactly.

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

4.3 Contraindications

Desflurane is contraindicated in patients with hypersensitivity to the active substance or known sensitivity to halogenated agents.

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

Must not be used in patients with known or genetic susceptibility to malignant hyperthermia (see also section 4.4)

Desflurane should not be used in patients 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 must 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.

Desflurane should not be used 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

Malignant hyperthermia
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 signalled by hypercapnia, and may include body temperature elevation, muscle rigidity, tachycardia, tachypnoea, 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 must not be used in subjects known to be susceptible to malignant hyperthermia. Fatal outcome of malignant hyperthermia has been reported with desflurane.

Perioperative hyperkalaemia
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 (see section 4.8). Patients with latent as well as overt muscular dystrophies, particularly Duchenne muscular dystrophy, appear to be most vulnerable. Concomitant use of suxamethonium chloride has been associated with most, but not all, of these cases. These patients also experienced significant elevations in serum creatinine kinase levels and, in some cases, changes in urine consistent with myoglobinuria. Despite the similarity in presentation to malignant hyperthermia, none of these patients exhibited signs or symptoms of muscle rigidity or hypermetabolic state.

Early and aggressive intervention to treat the hyperkalemia and resistant arrhythmias is recommended, as is subsequent evaluation for latent neuromuscular disease.

Use in Children and adolescents with Bronchial Hyperreactivity
Desflurane should be used with caution in children and adolescents 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
Due to the limited data available in non-intubated paediatric patients, desflurane is not approved for maintenance of anaesthesia in non-intubated children. Caution should be exercised should desflurane be used for maintenance anaesthesia with laryngeal mask airway

(LMA) in particular for children 6 years old or younger because of the increased potential for adverse respiratory reaction, e.g. coughing and laryngospasm, especially with removal of the LMA under deep anaesthesia.

Obstetrics
Due to the limited number of patients studied, desflurane is not recommended for use in obstetric procedures. Desflurane should not be used in pregnant patients due to halogenated anesthetics are uterine-relaxant and reduces the uterine-placental blood-flow (see section 4.6).

QT Prolongation
QT prolongation, very rarely associated with torsade de pointes, has been reported (see section 4.8). Caution should be exercised when administering desflurane to susceptible patients (e.g. patients with congenital Long QT Syndrome or patients taking drugs with the ability to prolong the QT interval).

Precautions:

Liver disease
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, which rarely can cause hepatic failure and liver necrosis. Cirrhosis, viral hepatitis or other pre-existing hepatic disease may be a reason to select an anaesthetic other than a halogenated anaesthetic.

Increased cerebral oedema
Desflurane, as other volatile anaesthetics, may increase the cerebrospinal fluid pressure 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.

Monitoring of Blood pressure and Heart rate
In patients with coronary artery disease, maintenance of normal haemodynamics is important to avoid myocardial ischemia. A rapid increase in desflurane concentration is associated with a marked increase in pulse rate, mean arterial pressure and circulating levels of adrenalin and noradrenalin. Desflurane should be used with other medications, preferably intravenous opioids and hypnotics.

Hypotensive and hypovolaemic patients
Blood pressure and heart rate shall be monitored closely during maintenance of anaesthesia in order to evaluate the depth 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 to hypovolemic, hypotensive and weakened patients is not investigated adequately. As for other potent anaesthetic agents for inhalation, a lower concentration is recommended for these patients.

Use with carbon dioxide (CO_2)
Desflurane can react with desiccated carbon dioxide (CO_2) absorbents in re-circulation anaesthesia systems to produce carbon monoxide that may result in elevated levels of

carboxyhaemoglobin in some patients. Therefore, only fresh (moist) CO_2 absorbents should be used. 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 re-placed before the administration of desflurane.

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.

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

As with other volatile anaesthetics, antiemetics are recommended for patients with moderate and high risk for postoperative nausea and vomiting.

A specific recommendation for repeated anaesthesia cannot be made due to insufficient experience. As with all halogenated anaesthetics, repeated anaesthesia within a short period of time should be approached with caution.

Desflurane shall not be administered to patients that are inclined to develop bronchial contraction, as bronchial spasms may occur.

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 in section 4.2).

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 suxamethonium chloride by approximately 30% and that of atracurium by approximately 50% compared to N_2O/opioid anaesthesia. The doses ofatracurium, rocuronium and other muscle relaxants needed to produce 95% (ED_{95}) depression in neuromuscular transmission at different concentrations of desflurane are given in Table 2. 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		**Atracurium**	**Suxa-methonium**	**Vecu-ronium**	**Rocu-ronium**	**Cisa-tricurium**	**Miva-curium**
0,65 MAC/ 60 % N_2O/O_2		0,133	*NA	*NA	*NA	*NA	*NA
1,25 MAC/ 60 % N_2O/O_2		0,119	*NA	*NA	*NA	*NA	*NA
1,25 MAC/O_2		0,120	0,360	0,019	*NA	*NA	*NA

100 % O_2							
1,3 MAC/ 30 % O_2 in air		*NA	*NA	*NA	*NA	0,0238	*NA
1,5 MAC/ 70 % N_2O/O_2		*NA	*NA	*NA	0.19	0,034	0,058

*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 and opioids
Patients anesthetised with different concentrations of desflurane who received increasing doses of intravenous fentanyl or intravenous midazolam showed a reduction in the anaesthetic requirements or MAC. Results are reported in Table 3. There is similar influence on MAC with other opioid and sedative drugs, such as remifentanil, dexmedetomidine and droperidol.

Table 3
Effect of Fentanyl or Midazolam on Desflurane

Medication	*MAC (%)	% MAC-reduction
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

* Includes values for ages 18-65 years

4.6 Fertility, pregnancy and lactation

Pregnancy
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.
There are no adequate data from the use of desflurane in pregnant or lactating women; therefore, desflurane is not indicated for use during pregnancy (see section 4.4).
Studies in animals have shown reproductive toxicity (see section 5.3).

Breastfeeding
Desflurane is not indicated for use in lactating women. It is unknown whether desflurane is excreted in human milk.

Fertility

There are no data on effects on fertility in humans.

4.7 Effects on ability to drive and use machines

Patients should be advised that the ability to perform tasks such as driving or operation of machinery due to the sedation and loss of consciousness is 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 cardiorespiratory 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),
- Not known (cannot be estimated from the available data)

Adverse Reactions		
System Organ Class (SOC)	**Preferred MedDRA Term**	**Frequency**
Investigations	Increased creatinine phosphokinase	Common
	ECG abnormal	Common
	Electrocardiogram ST-T change	Not known
	Electrocardiogram T wave inversion	Not known
	Transaminases (alanine and aspartate aminotransferase) increased	Not known
	Aspartate aminotransferase increased	Not known
	Coagulation test abnormal	Not known
	Ammonia increased	Not known
	Blood bilirubin increased	Not known
Cardiac Disorders	Nodal arrhythmia	Common
	Bradycardia	Common
	Tachycardia	Common
	Hypertension	Common
	Myocardial infarction	Uncommon
	Myocardial ischaemia	Uncommon
	Arrythmia	Uncommon
	Cardiac arrest	Not known
	Torsade de pointes	Not known
	Ventricular failure	Not known
	Ventricular hypokinesia	Not known
	Atrial fibrillation	Not known
Blood and lymphatic system disorders	Coagulopathy	Not known
Nervous System Disorders	Headache	Common
	Dizziness	Uncommon
	Convulsions	Not known

Adverse Reactions		
System Organ Class (SOC)	**Preferred MedDRA Term**	**Frequency**
Eye Disorders	Conjunctivitis	Common
	Ocular icterus	Not known
Respiratory, Thoracic and Mediastinal Disorders	Apnoea[+]	Common
	Cough[+]	Common
	Laryngospasm[°]	Common
	Hypoxia[+]	Uncommon
	Respiratory arrest	Not known
	Respiratory failure	Not known
	Respiratory distress	Not known
	Bronchospasm	Not known
	Haemoptysis	Not known
Gastrointestinal Disorders	Vomiting[+]	Very Common
	Nausea[+]	Very Common
	Salivary hypersecretion[+]	Common
	Pancreatitis acute	Not known
	Abdominal pain	Not known
Skin and Subcutaneous Tissue Disorders	Urticaria	Not known
	Erythema	Not known
Musculoskeletal and Connective Tissue Disorders	Myalgia	Uncommon
	Rhabdomyolysis	Not known
Metabolism and nutrition disorders	Hyperkalaemia	Not known
	Hypokalaemia	Not known
	Metabolic acidosis	Not known
Infections and infestations	Pharyngitis	Common
Injury, poisoning and procedural complications[*]	Dizziness[*]	Not known
	Migraine[*]	Not known
	Tachyarrhythmia[*]	Not known
	Palpitations[*]	Not known
	Eye burns[*]	Not known
	Blindness transient[*]	Not known
	Encephalopathy[*]	Not known
	Ulcerative keratitis[*]	Not known
	Ocular hyperaemia[*]	Not known
	Visual acuity reduced[*]	Not known
	Eye irritation[*]	Not known
	Eye pain[*]	Not known
	Fatigue[*]	Not known
	Skin burning sensation[*]	Not known
Vascular disorders	Vasodilation	Uncommon
	Malignant hypertension	Not known
	Haemorrhage	Not known
	Hypotension	Not known
	Shock	Not known
General disorders and Administration Site Conditions	Hyperthermia malignant	Not known
	Asthenia	Not known
	Malaise	Not known

Adverse Reactions		
System Organ Class (SOC)	**Preferred MedDRA Term**	**Frequency**
Hepatobiliary disorders	Hepatic failure	Not known
	Hepatic necrosis	Not known
	Hepatitis	Not known
	Cytolytic hepatitis	Not known
	Cholestasis	Not known
	Jaundice	Not known
	Hepatic function abnormal	Not known
	Liver disorder	Not known
Psychiatric disorders	Breath holding[+]	Common
	Agitation	Uncommon
	Post-operative agitation	Not known

° reported during induction with desflurane.
[+] reported during induction and maintenance with desflurane.
[*] Reactions was due to accidental exposures to non- patients.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 the national reporting system listed in Appendix V.

4.9 Overdose

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 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:

1. Discontinue or minimize exposure to desflurane.
2. Establish an airway and initiate assisted or controlled ventilation with 100% oxygen.
3. Support and maintain adequate haemodynamics.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anaesthetics, halogenated hydrocarbons and ATC code: N01AB07.

Mechanism of action and Pharmacodynamic effects:
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. As suggested by its structure, the 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. The duration of anaesthesia and selected recovery measures for desflurane from clinical studies are given in the following tables:

Clinical efficacy and safety in adults and the paediatric population:

In 178 female outpatients undergoing laparoscopy, premedicated with fentanyl (1.5-2.0 μg/kg), anaesthesia was initiated with propofol 2.5 mg/kg, desflurane/N_2O 60% in O_2 or desflurane/O_2 alone. Anaesthesia was maintained with either propofol 1.5-9.0 mg/kg/hr, desflurane 2.6-8.4% in N_2O 60% in O_2, or desflurane 3.1-8.9% in O_2.

Emergence and Recovery After Outpatient Laparoscopy
178 Females, Ages 20-47
Times in Minutes: Mean ± SD (Range)

Induction:	**Propofol**	**Propofol**	**Desflurane/N_2O**	**Desflurane/O_2**
Maintenance:	**Propofol/N_2O**	**Desflurane/N_2O**	**Desflurane/N_2O**	**Desflurane/O_2**
Number of Pts:	**N = 48**	**N = 44**	**N = 43**	**N = 43**
Median age	30 (20 - 43)	26 (21 - 47)	29 (21 - 42)	30 (20 - 40)
Anesthetic time	49 ± 53 (8 - 336)	45 ± 35 (11 - 178)	44 ± 29 (14 - 149)	41 ± 26 (19 - 126)
Time to open eyes	7 ± 3 (2 - 19)	5 ± 2* (2 - 10)	5 ± 2* (2 - 12)	4 ± 2* (1 - 11)
Time to state name	9 ± 4 (4 - 22)	8 ± 3 (3 - 18)	7 ± 3* (3 - 16)	7 ± 3* (2 - 15)
Time to stand	80 ± 34 (40 - 200)	86 ± 55 (30 - 320)	81 ± 38 (35 - 190)	77 ± 38 (35 - 200)
Time to walk	110 ± 6 (47 - 285)	122 ± 85 (37 – 375)	108 ± 59 (48 - 220)	108 ± 66 (49 - 250)
Time to fit for discharge	152 ± 75 (66 - 375)	157 ± 80 (73 - 385)	150 ± 66 (68 - 310)	155 ± 73 (69 - 325)

*Differences were statistically significant ($p<0.05$) by Dunnett's procedure comparing all treatments to the propofol-propofol/N_2O (induction and maintenance) group. Results for comparisons greater than one hour after anaesthesia show no differences between groups and considerable variability within groups.

In 88 un-premedicated outpatients, anaesthesia was initiated with thiopental 3-9 mg/kg or desflurane in O_2. Anaesthesia was maintained with isoflurane 0.7-1.4% in N_2O 60%, desflurane 1.8-7.7% in N_2O 60%, or desflurane 4.4-11.9% in O_2.

Emergence and Recovery Times in Outpatient Surgery
46 Males, 42 Females, Ages 19-70
Times in Minutes: Mean ± SD (Range)

Induction:	**Thiopental**	**Thiopental**	**Thiopental**	**Desflurane/O_2**
Maintenance:	**Isoflurane/N_2O**	**Desflurane/N_2O**	**Desflurane/O_2**	**Desflurane/O_2**
Number of Pts:	**N = 23**	**N = 21**	**N = 23**	**N = 21**
Median age	43 (20 - 70)	40 (22 - 67)	43 (19 - 70)	41 (21-64)
Anesthetic time	49 ± 23 (11 - 94)	50 ± 19 (16 - 80)	50 ± 27 (16 - 113)	51 ± 23 (19 - 117)
Time to open eyes	13 ± 7 (5 - 33)	9 ± 3* (4 - 16)	12 ± 8 (4 - 39)	8 ± 2* (4 - 13)
Time to state name	17 ± 10 (6 - 44)	11 ± 4* (6 - 19)	15 ± 10 (6 - 46)	9 ± 3* (5 - 14)
Time to walk	195 ± 67 (124 - 365)	176 ± 60 (101 - 315)	168 ± 34 (119 - 258)	181 ± 42 (92 - 252)
Time to fit for discharge	205 ± 53 (153 - 365)	202 ± 41 (144 - 315)	197 ± 35 (155 - 280)	194 ± 37 (134 - 288)

*Differences were statistically significant ($p<0.05$) by Dunnett's procedure comparing all treatments to the thiopental-isoflurane/N_2O (induction and maintenance) group. Results for comparisons greater than one hour after anaesthesia show no differences between groups and considerable variability within groups.

SUPRANE was studied in twelve volunteers receiving no other drugs. Haemodynamic effects during controlled ventilation ($PaCO_2$ 38 mm Hg) were:

Haemodynamic Effects of Desflurane During Controlled Ventilation
12 Male Volunteers, Ages 16-26
Mean ± SD (Range)

Total MAC Equivalent	End-Tidal % Des/O_2	End-Tidal % Des/N_2O	Heart Rate (beats/min)		Mean Arterial Pressure (mm Hg)		Cardiac Index (L/min/m^2)	
			O_2	N_2O	O_2	N_2O	O_2	N_2O
0	0% / 21%	0% / 0%	69 ± 4 (63 - 76)	70 ± 6 (62 - 85)	85 ± 9 (74 - 102)	85 ± 9 (74 - 102)	3.7 ± 0.4 (3.0 - 4.2)	3.7 ± 0.4 (3.0 - 4.2)
0.8	6% / 94%	3% / 60%	73 ± 5 (67 - 80)	77 ± 8 (67 - 97)	61 ± 5* (55 - 70)	69 ± 5* (62 - 80)	3.2 ± 0.5 (2.6 - 4.0)	3.3 ± 0.5 (2.6 - 4.1)
1.2	9% / 91%	6% / 60%	80 ± 5* (72 - 84)	77 ± 7 (67 - 90)	59 ± 8* (44 - 71)	63 ± 8* (47 - 74)	3.4 ± 0.5 (2.6 - 4.1)	3.1 ± 0.4* (2.6 - 3.8)
1.7	12% / 88%	9% / 60%	94 ± 14* (78 - 109)	79 ± 9 (61 - 91)	51 ± 12* (31 - 66)	59 ± 6* (46 - 68)	3.5 ± 0.9 (1.7 - 4.7)	3.0 ± 0.4* (2.4 - 3.6)

*Differences were statistically significant ($p<0.05$) compared to awake values, Newman-Keul's method of multiple comparison.

The use of desflurane concentrations higher than 1.5 MAC may produce apnoea.

5.2 Pharmacokinetic properties

Absorption, distribution and biotransformation:
Desflurane induces a rapid induction of anaesthesia without metabolism in liver or other organs and with minimal build up in fat tissue.

Elimination:
Desflurane is eliminated primarily unchanged via the lungs.

Pharmacokinetic parameters:
In surgery patients during a constant inhalation of 6% desflurane with a flow rate of 4-6L/min, the observed pharmacokinetics parameters (mean±SD) are Cmax 207.2±26.7 µg/mL, Tmax 25.0±5.5 min, AUC_{0-t} 6786.2±926.5 µg*min/mL and $T_{½}$ was 25.7± 6.3 min.

5.3 Preclinical safety data

No mutagenicity or teratogenicity.

No teratogenicity effect in rats and rabbits was observed after approximately 10 and 13 cumulative MAC-hours desflurane exposure under ontogenesis. Embryotoxicity was seen after toxic exposure during pregnancy, possibly due to the pharmacologic maternal effect of desflurane.

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 in not known.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

None

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in upright position with cap firmly in place. This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

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.

Pack sizes of 1 and 6 bottles.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Replace cap after use.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

<To be completed nationally>

8. MARKETING AUTHORISATION NUMBER

<To be completed nationally>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<To be completed nationally>

10. DATE OF REVISION OF THE TEXT

September 2022