SCHEDULING STATUS

S5

PROPRIETARY NAME (and dosage form)

TORRANE ™ (liquid for inhalation)

COMPOSITION

Each 250 ml bottle of **TORRANE ™** contains 250 ml desflurane

PHARMACOLOGICAL CLASSIFICATION

A. 2.1 Anaesthetics

PHARMACOLOGICAL ACTION

Desflurane is a volatile halogenated anaesthetic with a chemical structure similar to isoflurane, except for substitution of a fluorine atom for chlorine at the alpha-ethyl carbon. It produces a dose-related, reversible loss of consciousness, modification of autonomic reflexes and depression of respiration and the cardiovascular system. Desflurane has low solubility in blood and tissues and is relatively resistant to degradation which minimise the risk of nephrotoxicity. Desflurane is nonflammable and non-explosive in mixtures of air or oxygen.

Pharmacokinetics

Desflurane has a low blood/gas partition coefficient and on inhalation, its absorption, distribution, and elimination are reported to be rapid. It is excreted mainly unchanged through the lungs. A small amount diffuses through the skin. About 0,02 % of inhaled desflurane is metabolised in the liver and trichloroacetic acid has been detected in the serum and urine of patients given desflurane. Within five minutes of administration, the alveolar concentration reaches 80 % of the inspired concentration.

INDICATIONS

TORRANE™ is used for induction and maintenance of general anaesthesia in adults and for the maintenance of anaesthesia in infants and children. **TORRANE™** is not recommended for induction in children due to its pungency.

CONTRA-INDICATIONS

- **TORRANE™** is contra-indicated in patients with hypersensitivity to desflurane or other halogenated agents.
- **TORRANE™** is an irritant to the airways and may provoke breath holding, apnoea, coughing, increased salivation and laryngospasm. It is therefore not recommended for induction of anaesthesia in paediatric patients (younger than 12 years old).
- Patients with known or suspected susceptibility to malignant hyperthermia should not be anaesthetized with **TORRANE™**.
- **TORRANE™** may increase CSF pressure and should therefore be used with caution in patients with, or at risk from, raised intracranial pressure.

WARNINGS AND SPECIAL PRECAUTIONS

- Because of the low boiling-point **TORRANE™** of it must be delivered by a special heated and pressurized vaporiser, preferably within a closed circuit system.
- Only persons trained in the administration of general anaesthesia may administer **TORRANE™**. Facilities for maintenance of a patent airway, oxygen enrichment, artificial ventilation, and circulatory resuscitation must be immediately available.
- Hypotension and respiratory depression increase as anaesthesia is deepened.
- **TORRANE™** is not recommended for induction of anaesthesia in children under 12 years due to the high incidence of adverse effects (see **CONTRA-INDICATIONS**).
- **TORRANE™** should be used in combination with intravenous opioids and hypnotics in patients with coronary artery disease or other conditions where increases in heart rate or blood pressure are undesirable.

- **TORRANE™** may cause dose-dependent increases in cerebrospinal fluid pressure in patients with space occupying lesions. In such patients **TORRANE™** should be administered at 0,8 MAC (minimum alveolar concentration) or less, and in conjunction with a barbiturate or propofol induction and hyperventilation (hypocapnia) in the period before cranial decompensation. Appropriate attention must be paid to maintain cerebral perfusion pressure.
- A lower concentration of **TORRANE ™** is recommended in hypovolaemic, hypotensive and debilitated patients.
- **TORRANE ™** is a potential trigger of malignant hyperthermia. If malignant hyperthermia unexpectedly occurs the triggering agent must be discontinued, dantrolene sodium will be indicated for reversal of this hyperthermia.
- **TORRANE ™** is not recommended for use in obstetric operations.
- Disruptions of the liver function, icterus and fatal liver necrosis have been reported with the use of halogenated anaesthetics. These reactions appear to indicate hypersensitivity reactions to anaesthetics. Cirrhosis, viral hepatitis or other pre-existing liver disease can be a reason to select an anaesthetic other than a halogenated anaesthetic.

INTERACTIONS

The effects of competitive neuromuscular blockers such as atracurium, pancuronium, suxamethonium, and vecuronium are enhanced by **TORRANE ™.** The doses needed to produce 95 % (ED_{95})

depression in neuromuscular transmission at different concentrations of **TORRANE ™** are given in table 1. The ED_{95} of vecuronium is 14 % lower with **TORRANE ™** than isoflurane and recovery from neuromuscular blockade is longer with **TORRANE ™** than with isoflurane.

Table 1: Dosage (mg/kg) of muscle relaxant causing 95 % depression in neuromuscular transmission

TORRANE ™	**Pancuronium**	**Atracurium**	**Suxamethonium**	**Vecuronium**
0,65 MAC/60 % N_2 0/0_2	0,026	0,123	*NA	*NA
1,25 MAC/60 % $N_2$0/0_2	0,018	0,091	*NA	*NA
1,25 MAC/0_2	0,022	0,120	0,362	0,019

*NA = not available

- Lower doses of **TORRANE ™** are required in those receiving opioids, benzodiazepines or other sedatives.
- Patients anaesthetised with different concentrations of **TORRANE ™** who received increasing doses of fentanyl showed a marked reduction in the anaesthetic requirements or MAC (minimum alveolar concentration).
- The administration of increasing doses of intravenous midazolam showed a small reduction in MAC. Results are reported in table 2. It is anticipated that there will be a similar influence on MAC with other opioid and sedative drugs.

Table 2: TORRANE ™ 0,6-0,8 MAC/0_2

	***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

- Care is advised if adrenaline or other sympathomimetics are given to patients during desflurane anaesthesia.
- An excessive prolongation of neuromuscular blocking effects occurs when **TORRANE™** is used in combination with cisatracurium or rapacuronium.
- St John's Wort use prior to surgery using anaesthesia has been associated with complications such as hypotension and delayed emergence from anaesthesia. To avoid complications, it is recommended to discontinue St John's Wort at least 5 days prior to the use of anaesthesia.
- When succinylcholine is given concurrently with anaesthetic agents, the neuromuscular blocking effect of succinylcholine may be enhanced. Co-administration of succinylcholine and **TORRANE™** should be used with caution.
- When used concomitantly, verapamil and **TORRANE™** should each be carefully titrated to avoid excessive cardiovascular depression.

PREGNANCY AND LACTATION

The safety in pregnancy and lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE

TORRANE™ is administered by inhalation.

TORRANE™ should be delivered from a vaporiser specifically designed and designated for use with **TORRANE™**

Dosage:

The minimum alveolar concentration (MAC) of **TORRANE™** is age-specific and has been determined as listed below:

AGE	**100 % OXYGEN**	**60 % NITROUS OXIDE/40 % Oxygen**
0 - 1 year	8,95 -10,65 %	5,75 - 7,75 % *
1 - 12 years	7,20 - 9,40 %	5,75 - 7,00 % **
18 - 30 years	6,35 - 7,25 %	3,75 - 4,25 %
30 - 65 years	5,75 - 6,25 %	1,75 - 3,25 %
over 65 years	5,17 ± 0,6 %	1,67 ± 0,4 %

*3-12 months ** 1-5 years

Opioids or benzodiazepines decrease the amounts of **TORRANE ™** required to produce anaesthesia.

TORRANE™ decreases the doses of neuromuscular blocking agents (see "INTERACTIONS").

Induction:

In adults a starting concentration of 3 % is recommended, increasing in 0,5-1,0 % increments every 2 to 3 breaths. Inspired concentrations of 4-11 % **TORRANE™** produce surgical anaesthesia in 2- 4 minutes. Higher concentrations up to 15 % may be used. Such concentrations of **TORRANE ™** will proportionately dilute the concentration of oxygen and commencing administration of oxygen should be 30 % or above. High concentrations of **TORRANE ™** may induce upper airway adverse events. After induction in adults with an intravenous drug such as thiopental or propofol, **TORRANE ™** can be started at approximately 0,5 -1 MAC, whether the carrier gas is oxygen or nitrous oxide/oxygen. **TORRANE ™** is not recommended for induction of general anaesthesia via mask in children because of the high incidence of laryngospasm, increase in secretions, breath holding and coughing.

Maintenance:

Surgical levels of anaesthesia may be sustained with a 2-6 % concentration of **TORRANE ™** when nitrous oxide is used concomitantly. **TORRANE ™** at 2,5-8,5 % may be required when administered using oxygen or oxygen enriched air. In children, surgical levels of anaesthesia may be maintained with concentrations of 5,2-10 % **TORRANE ™** with or without the concomitant use of nitrous oxide.

If high concentrations of **TORRANE ™** are used with nitrous oxide, it is important to ensure that the inspired mixture contains a minimum of 30 % oxygen.

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

Dosage in renal and hepatic impairment:

Concentrations of 1-4 % **TORRANE ™** 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.

SIDE EFFECTS

Cardiovascular effects:

Frequent: Alteration in heart rate, bradyarrhythmia, hypertension, hypotension, sinus arrhythmia, tachycardia

Less frequent: Abnormal ECG, cardiac dysrhythmia

Endocrine or Metabolic effects:

The following have been reported but the frequency is unknown:

Hyperkalaemia, malignant hyperthermia

Gastrointestinal disorders:

Frequent: Excessive salivation, nausea, vomiting

Haematological effects:

Frequent: Desaturation of blood, leucocytosis (transitory)

Hepatic effects:

Less frequent: Hepatic necrosis, hepatotoxicity, liver failure, hepatitis

Nervous system effects:

Frequent: Headache, vertigo

Less frequent: Dizziness, suppression of EEG activity

Musculoskeletal effects:

Less frequent: Myalgia

Ophthalmic effects:

Frequent: Conjunctival hyperaemia

Psychiatric effects:

Less frequent: Agitation

Respiratory effects:

Frequent: Apnoea, cough, excessive bronchial secretion, interrupted breathing, laryngeal spasm, pharyngitis, respiratory obstruction

Less frequent: Dyspnoea

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Human experience:

There is no experience of overdosage in humans.

Symptoms and treatment of *overdosage:*

The symptoms of overdosage of **TORRANE ™** are anticipated to be 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 **TORRANE ™** establish a clear airway and initiate assisted or controlled ventilation with pure oxygen. Support and maintain adequate haemodynamics.

IDENTIFICATION

TORRANE ™ is a clear, colourless volatile liquid.

PRESENTATION

TORRANE ™ is marketed in a 250 ml USP Type III amber glass bottle (PVC coated) with a polyethylene/EPDM/stainless steel closure and a EPDM/HDPE cap. The bottle closure is protected by a PVC heat-seal tubing.

STORAGE INSTRUCTIONS

Store at or below 25 °C. Do not refrigerate. Protect from light and moisture.

Keep in original container until immediately prior to use. It must be stored in tightly sealed bottles and is administered by inhalation.

KEEP OUT OF REACH OF CHILDREN.

Discard any unused portion.

REGISTRATION NUMBER

43/2.1/0392

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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