

NEW ZEALAND DATA SHEET

1. FORTHANE VOLATILE LIQUID FOR INHALATION 100%

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

FORTHANE is comprised only of the active ingredient isoflurane 100%.

3. PHARMACEUTICAL FORM

Volatile liquid for inhalation.

Isoflurane is a non-flammable liquid administered by vaporisation. It is a general inhalation anaesthetic medicine with a mildly pungent ethereal odour containing no additives or chemical stabilisers.

Isoflurane is identified chemically as 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether and its molecular weight is 184.5.

Some physical constants are:

Boiling point 760 mmHg	48.5°C	
Refractive index n_D^{20}	1.2990 – 1.3005	
Specific gravity 25°/25°C	1.496	
Vapour pressure in mmHg	18°C	218
	20°C	238
	22°C	261
	24°C	285
	25°C	295
	26°C	311
	30°C	367
	35°C	450

Equation for vapour pressure calculation:

$$\text{Log}_{10} P_{\text{vap}} = A + \frac{B}{T} \quad \text{where } A = 8.056$$
$$B = - 1664.58$$
$$T = \text{°C} + 273.16 \text{ (Kelvin)}$$

Partition coefficients @ 37°C:

Water/gas	0.61
Blood/gas	1.43
Oil/gas	90.80

Partition coefficients @ 25°C - rubber and plastic:

Conductive rubber/gas	62.0
Butyl rubber/gas	75.0
Polyvinyl chloride/gas	110.0
Polyethylene/gas approx.	2.0
Polyurethane/gas approx.	1.4
Polyolefin/gas approx.	1.1
Butyl acetate/gas approx.	2.5

Purity by gas chromatography	> 99.9%
Lower limit of flammability in oxygen or nitrous oxide at 9 joules/sec and 23°C	None
Lower limit of flammability in oxygen or nitrous oxide at 900 joules/sec and 23°C	Greater than useful concentration in anaesthesia

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Isoflurane may be used for induction and maintenance of general anaesthesia. This anaesthetic agent can also be used for sedation of ventilated patients in the intensive therapy unit for up to 48 hours.

4.2 Dose and method of administration

Vaporisers specially calibrated for isoflurane should be used so that the concentration of anaesthetic delivered can be accurately controlled.

General Anaesthesia

MAC values for isoflurane diminish with age, falling from an average in oxygen of 1.28% in the mid-twenties to 1.15% in the mid-forties, to 1.05% in the mid-sixties age group. For neonates, the MAC of isoflurane in oxygen is 1.6%, in infants aged 1 month to 6 months is 1.87%, and from 6 months to 12 months, 1.80%.

Premedication

Medicines used for premedication should be selected for the individual patient, bearing in mind the respiratory depressant effect of isoflurane. The use of anticholinergic medicines is a matter of choice.

Induction

A short-acting barbiturate or other intravenous induction agent is usually administered followed by inhalation of the isoflurane mixture. Alternatively, isoflurane with oxygen or with an oxygen/nitrous oxide mixture may be used.

It is recommended that induction with isoflurane be initiated at a concentration of 0.5%. Concentrations of 1.5-3.0% usually produce surgical anaesthesia in 7-10 minutes.

Maintenance

Surgical levels of anaesthesia may be maintained with 1.0-2.5% isoflurane in oxygen/nitrous oxide mixtures. An additional 0.5-1.0% isoflurane may be required when given with oxygen alone. If added relaxation is required, supplemental doses of muscle relaxant may be used.

Arterial pressure levels during maintenance tend to be inversely related to alveolar isoflurane concentrations in the absence of other complicating factors. Excessive falls in blood pressure may be due to depth of anaesthesia and, in these circumstances, should be corrected by reducing the inspired isoflurane concentration.

Sedation

Sedation may be maintained with 0.1 - 1.0% isoflurane in air/oxygen mixtures. This dose will need to be titrated to the requirements of the individual patients.

Use in Special Populations

Elderly

As with other agents, lesser concentrations of isoflurane are normally required to maintain surgical anaesthesia in elderly patients. See above and section 5.2 Pharmacokinetic properties for MAC values.

Paediatric population

Isoflurane may be used in neonates and infants under 2 years of age (see also section 4.4 Special warnings and precautions for use).

4.3 Contraindications

Isoflurane is contraindicated in patients with known sensitivity to isoflurane or other halogenated anaesthetics. It is also contraindicated in patients with known or suspected genetic susceptibility to malignant hyperthermia.

Isoflurane must not be used in patients who have developed an icterus and/or fever of unknown origin after administration of isoflurane or another halogenated anaesthetic.

4.4 Special warnings and precautions for use

General

As with any potent general anaesthetic, isoflurane should only be administered in an adequately equipped anaesthetising environment by those who are familiar with the pharmacology of the medicine, and qualified by training and experience to manage the anaesthetised patient. Since levels of anaesthesia may be altered quickly and easily with isoflurane, only vaporisers which deliver a predictable output with reasonable accuracy, or techniques during which inspired or expired concentrations can be monitored, should be used. The degree of hypotension and respiratory depression may provide some indication of anaesthetic depth.

Reports demonstrate that isoflurane can produce hepatic injury ranging from mild transient increases of liver enzymes to fatal hepatic necrosis in very rare instances. It has been reported that previous exposure to halogenated hydrocarbon anaesthetics, especially if the interval is less than 3 months, may increase the potential for hepatic injury.

Regardless of the anaesthetics employed, maintenance of normal haemodynamics is important to the avoidance of myocardial ischemia in patients with coronary artery disease.

As with other halogenated agents, isoflurane must be used with caution in patients with increased intracranial pressure. In such cases hyperventilation may be necessary.

The action of non-depolarising relaxants is markedly potentiated with isoflurane.

Isoflurane should be administered with caution to patients who can develop bronchoconstriction since bronchospasm can occur.

Isoflurane may cause respiratory depression, which may be augmented by narcotic premedication or other agents causing respiratory depression. Respiration should be supervised and if necessary, assisted.

Isoflurane markedly increases cerebral blood flow at deeper levels of anaesthesia. There may be a transient rise in cerebral spinal fluid pressure, which is fully reversible with hyperventilation.

Since levels of anaesthesia may be altered easily and rapidly, only vaporisers producing predictable concentrations and flow rates should be used. Hypotension and respiratory depression increase as anaesthesia is deepened.

Reports of QT prolongation, associated with torsade de pointes (in exceptional cases, fatal), have been received. Caution should be exercised when administering isoflurane to patients at risk for QT prolongation.

Caution should be exercised in administering general anaesthesia, including isoflurane, to patients with mitochondrial disorders.

Isoflurane, like other inhalational agents, has relaxant effects on the uterus with the potential risk for uterine bleeding. Clinical judgment should be observed when using isoflurane during obstetric anaesthesia. Consideration should be taken to use the lowest possible concentration of isoflurane in obstetrical operations.

Isolated cases of increased carboxyhaemoglobin have been reported with the use of fluorinated inhalation agents (i.e. desflurane, enflurane and isoflurane). No clinically significant concentrations of carbon monoxide are produced in the presence of normally hydrated absorbents. Care should be taken to follow manufacturers' instructions for CO₂ absorbents.

Replacement of Desiccated CO₂ Absorbents

Rare cases of extreme heat, smoke and/or spontaneous fire in the anaesthesia machine have been reported during administration of general anaesthesia with medicines in this class when used in conjunction with desiccated CO₂ absorbents, specifically those containing potassium hydroxide (e.g. Baralyme). When a clinician suspects that the CO₂ absorbent may be desiccated, it should be replaced before the administration of isoflurane. The colour indicator of most CO₂ absorbents does not necessarily change as a result of desiccation. Therefore, the lack of significant colour change should not be taken as an assurance of adequate hydration. CO₂ absorbents should be replaced routinely regardless of the state of the colour indicator.

Use in Children under 2 years of age

Isoflurane may be used in neonates and infants under 2 years of age with an acceptable margin of efficacy and safety and is compatible with all medicines commonly used in anaesthetic practice.

Malignant hyperthermia

In susceptible individuals, isoflurane anaesthesia may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. The syndrome includes nonspecific features such as muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and unstable blood pressures. (It should also be noted that many of these nonspecific signs may appear with light anaesthesia, acute hypoxia, etc.). PaO₂ and pH may decrease, and hyperkalemia and a base deficit may appear.

There have been postmarketing reports of malignant hyperthermia. Some of these reports have been fatal.

Treatment includes discontinuance of triggering agents (e.g. isoflurane), intravenous administration of dantrolene sodium, and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support as indicated, and management of electrolyte-fluid-acid-base derangements. (Consult prescribing information for

intravenous dantrolene sodium for additional information on patient management). Renal failure may appear later, and urine flow should be sustained if possible.

Perioperative Hyperkalaemia

Hyperkalaemic Cardiac Arrest in Paediatric Patients

Use of inhaled anaesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in paediatric patients during the postoperative period. Patients with latent as well as overt neuromuscular disease, particularly Duchenne muscular dystrophy, appear to be most vulnerable. Concomitant use of succinylcholine has been associated with most, but not all, of these cases. These patients also experienced significant elevations in serum creatine 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 hyperkalaemia and resistant arrhythmias is recommended, as is subsequent evaluation for latent neuromuscular disease.

Information to patients

Isoflurane, as well as other general anaesthetics, may cause a slight decrease in intellectual function for 2-4 days following anaesthesia. As with other anaesthetics, small changes in moods and symptoms may persist for up to 6 days after administration (see section 4.7 Effects on ability to drive and use machines).

4.5 Interaction with other medicines and other forms of interaction

Concomitant use of succinylcholine with inhaled anaesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in paediatric patients during the postoperative period.

All commonly used muscle relaxants are markedly potentiated by isoflurane, the effect being most profound with non-depolarising agents. Neostigmine reverses the effects of non-depolarising muscle relaxants but has no effect on the relaxant properties of isoflurane itself. All commonly used muscle relaxants are compatible with isoflurane.

Beta-sympathomimetic agents like isoprenaline and alpha- and beta-sympathomimetic agents like adrenaline and noradrenaline should be used with caution during isoflurane narcosis, due to a potential risk of ventricular arrhythmia.

Non-selective MAO-inhibitors: Risk of crisis during the operation. It is generally recommended that treatment should be stopped 2 weeks prior to surgery.

Medicinal products and compounds that increase the activity of cytochrome P450 isoenzyme CYP2E1, such as isoniazid and alcohol, may increase the metabolism of isoflurane and lead to significant increases in plasma fluoride concentrations.

Concomitant use of isoflurane and isoniazid can increase the risk of potentiation of the hepatotoxic effects.

Isoflurane may lead to marked hypotension in patients treated with calcium antagonists, in particular dihydropyridine derivatives.

Caution should be exercised when calcium antagonists are used concomitantly with inhalation anaesthetics due to the risk of additive negative inotropic effect.

Opioids, benzodiazepines and other sedative agents are associated with respiratory depression. Caution should be exercised when these agents are concomitantly administered with isoflurane.

4.6 Fertility, pregnancy and lactation

Fertility

Studies with the rat demonstrated no effect on fertility.

Pregnancy

Pregnancy Category B3.

Reproduction studies have been carried out on animals after repeated exposure to anaesthetic concentrations of isoflurane. Isoflurane has been shown to have a possible anaesthetic-related foetotoxic effect in mice when given in sub-therapeutic doses. Studies with the rat demonstrated no effect on pregnancy or delivery or on the viability of the offspring. No evidence of teratogenicity was revealed. Comparable experiments in rabbits produced similar negative results. The relevance of these studies to humans is not known, as there are no adequate and well-controlled studies in pregnant women.

Isoflurane should only be used during pregnancy if the benefit outweighs the potential risk.

Isoflurane, like other inhalational agents, has relaxant effects on the uterus with the potential risk for uterine bleeding. Clinical judgment should be observed when using isoflurane during obstetric anaesthesia. Consideration should be taken to use the lowest possible concentration of isoflurane in obstetrical operations.

Published animal studies of some anaesthetic/sedation drugs have reported adverse effects on brain development in early life (see section 5.3 Preclinical safety data).

Use in Caesarean section

Isoflurane, in concentrations up to 0.75%, has been shown to be safe and efficacious for the maintenance of anaesthesia for Caesarean section.

Breastfeeding

It is not known whether this medicine is excreted in human milk. Because many medicines are excreted in human milk, caution should be exercised when isoflurane is administered to a nursing woman.

4.7 Effects on ability to drive and use machines

Patients should be advised that performance of activities requiring mental alertness, such as operating a motor vehicle or hazardous machinery, may be impaired for 2-4 days after anaesthesia with isoflurane. As with other anaesthetics, small changes in moods and symptoms may persist for up to 6 days after administration (see section 4.4 Special warnings and precautions for use).

4.8 Undesirable effects

Adverse reactions encountered in the administration of isoflurane are in general dose-dependent extensions of pharmacophysiologic effects and include respiratory depression, hypotension and arrhythmias. Potential serious undesirable effects include malignant hyperthermia, hyperkalaemia, elevated serum creatine kinase, and myoglobinuria (see section 4.4 Special warnings and precautions for use).

Cardiac arrest, bradycardia, and tachycardia have been observed with general inhalation anaesthetic medicines including isoflurane.

Reports of QT prolongation, associated with torsade de pointes (in exceptional cases, fatal), have been received.

Bronchospasm and laryngospasm due to airway irritation have been reported with volatile anaesthetics during inhalation.

Electroencephalographic changes and convulsions have been observed with isoflurane.

Isolated cases of increased carboxyhaemoglobin have been reported with the use of fluorinated inhalation agents (i.e., desflurane, enflurane and isoflurane).

Isoflurane, like other inhalational agents, has relaxant effects on the uterus with the potential risk for uterine bleeding.

Shivering, nausea, vomiting, ileus, agitation, and delirium have been observed in the postoperative period.

Transient increases in blood bilirubin, blood glucose and serum creatinine with decrease in BUN, serum cholesterol and alkaline phosphatase have been observed. As with all other general anaesthetics, transient elevations in white blood count have been observed even in the absence of surgical stress.

Rare reports of hypersensitivity (including dermatitis contact, rash, dyspnoea, wheezing, chest discomfort, swelling face, or anaphylactic reaction) have been received, especially in association with long-term occupational exposure to inhaled anaesthetic agents, including isoflurane. These reactions have been confirmed by clinical testing (e.g. methacholine challenge). The aetiology of anaphylactic reactions experienced during inhalational anaesthetic exposure is, however, unclear because of the exposure to multiple concomitant medicines, many of which are known to cause such reactions.

Isoflurane potentiates the muscle relaxant effect of all muscle relaxants, most notably non-depolarising muscle relaxants, and MAC (minimum alveolar concentration) is reduced by concomitant administration of N₂O in adults.

Isoflurane may cause irritation of the airway.

Reports demonstrate that isoflurane can produce hepatic injury ranging from mild transient increases of liver enzymes to fatal hepatic necrosis in very rare instances.

Minimally raised levels of serum inorganic fluoride occur during and after isoflurane anaesthesia, due to biodegradation of the agent. It is unlikely that the low levels of serum inorganic fluoride observed could cause renal toxicity, as these are well below the proposed threshold levels for kidney toxicity.

Paediatric population

Use of inhaled anaesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in paediatric patients during the post-operative period (see section 4.4 Special warnings and precautions for use).

Other special populations

Neuromuscular disease:

Use of inhaled anaesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in paediatric patients during the post-operative period. Patients with latent as well as overt neuromuscular disease, particularly Duchenne muscular dystrophy, appear to be most vulnerable. Early and aggressive intervention to treat the hyperkalaemia and resistant arrhythmias is recommended, as is subsequent evaluation for latent neuromuscular disease (see section 4.4 Special warnings and precautions for use).

Reporting of Suspected Adverse Reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to <https://nzphvc.otago.ac.nz/reporting/>.

4.9 Overdose

In the event of overdosage, or what may appear to be overdosage, stop medicine administration, establish a clear airway and initiate assisted or controlled ventilation with pure oxygen.

Hypotension and respiratory depression have been observed. Close monitoring of blood pressure and respiration is recommended. Supportive measures may be necessary to correct hypotension and respiratory depression resulting from excessively deep levels of anaesthesia.

For advice on the management of overdose, please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anaesthetics, general – ATC code: N01A

Isoflurane is a general inhalation anaesthetic.

Induction and, particularly, recovery are rapid. Although slight pungency may limit the rate of induction, excessive salivation and tracheobronchial secretions do not appear to be stimulated. Pharyngeal and laryngeal reflexes are diminished quickly. Levels of anaesthesia may be changed rapidly with isoflurane. Heart rhythm remains stable. Spontaneous respiration becomes depressed as depth of anaesthesia increases and should be closely monitored and supported when necessary.

During induction, there is a decrease in blood pressure, which returns towards normal with surgical stimulation.

Blood pressure tends to fall during maintenance in direct relation to depth of anaesthesia, but cardiac rhythm remains stable. With controlled respiration and normal PaCO₂, cardiac output tends to be maintained despite increasing depth of anaesthesia primarily through a rise in heart rate, which compensates for a reduction in stroke volume. With spontaneous respiration, the resulting hypercapnia may increase heart rate and cardiac output above awake levels.

Cerebral blood flow remains unchanged during light isoflurane anaesthesia but tends to rise at deeper levels. Increases in cerebrospinal fluid pressure may be prevented or reversed by hyperventilating the patient before or during anaesthesia.

Electroencephalographic changes and convulsions are extremely rare with isoflurane. In general, isoflurane produces an EEG pattern similar to that seen with other volatile anaesthetics.

Isoflurane appears to sensitise the myocardium to adrenaline. Limited data suggest that subcutaneous infiltration of up to 50 mL of 1:200,000 solution adrenaline does not induce ventricular arrhythmias in patients anaesthetised with isoflurane.

Muscular relaxation may be adequate for some intra-abdominal operations at normal levels of anaesthesia, but should greater relaxation be required small doses of intravenous muscle relaxants may be used.

Isoflurane may be used for the induction and maintenance of general anaesthesia. Adequate data are not available to establish its place in pregnancy.

Paediatric population

Isoflurane may be used in neonates and infants under 2 years of age. See also section 4.4 Special warnings and precautions for use.

Paediatric Clinical Safety

Some published studies in children have observed cognitive deficits after repeated or prolonged exposures to anaesthetic agents early in life. These studies have substantial limitations, and it is not clear if the observed effects are due to the anaesthetic/sedation drug administration or other factors such as the surgery or underlying illness. In addition, more recent published registry studies did not confirm these findings.

Published animal studies of some anaesthetic/sedation drugs have reported adverse effects on brain development in early life (see Section 5.3 Preclinical safety data).

5.2 Pharmacokinetic properties

Absorption

M.A.C. (minimum alveolar concentration) in man:

Age	100% Oxygen	70% N ₂ O
0 – 1 mo. (neonate)	1.60%	
1 – 6 mos.	1.87%	
6 – 12 mos.	1.80%	
1 – 5 yrs.	1.60%	
26 ± 4 yrs.	1.28%	0.56%
44 ± 7 yrs.	1.15%	0.50%
64 ± 5 yrs.	1.05%	0.37%

Metabolism and Elimination

Relatively little metabolism of isoflurane occurs in the human body. In the postoperative period only 0.17% of the isoflurane taken up can be recovered as urinary metabolites. Peak serum inorganic fluoride values usually average less than 5 micromole/litre and occur about four hours after anaesthesia, returning to normal levels within 24 hours. No signs of renal injury have been reported after isoflurane administration.

Known metabolites of isoflurane have been found to be either nontoxic or present in too low a concentration to be harmful.

5.3 Preclinical safety data

Published studies in pregnant and juvenile animals suggest that the use of anaesthetic and sedation drugs that block NMDA receptors and/or potentiate GABA activity during the period of rapid brain growth or synaptogenesis may result in neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis when used for longer than 3 hours.

These studies included anaesthetic agents from a variety of drug classes. The clinical significance of these nonclinical findings is yet to be determined (see Section 5.1 Pharmacodynamic properties - Description of Clinical Studies, Safety).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

Isoflurane has been reported to interact with dry carbon dioxide absorbents to form carbon monoxide. In order to minimise the risk of formation of carbon monoxide in rebreathing circuits and the possibility of elevated carboxyhaemoglobin levels, carbon dioxide absorbents should not be allowed to dry out. (See also section 4.4 Special warnings and precautions for use).

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Store at room temperature (at or below 30°C). Isoflurane contains no additives and has been demonstrated to be stable for the period defined by the expiration dating on the label.

6.5 Nature and contents of container

Isoflurane is supplied in glass bottles containing 100 mL* and 250 mL (* not marketed in New Zealand).

6.6 Special precautions for disposal and other handling

Vaporisers specially calibrated for isoflurane should be used so that the concentration of anaesthetic delivered can be accurately controlled.

It is recommended that vapour from this and other inhalation agents be efficiently extracted from the area of use.

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

7. MEDICINE SCHEDULE

Prescription medicine.

8. SPONSOR

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9. DATE OF FIRST APPROVAL

4 August 1983.

10. DATE OF REVISION OF THE TEXT

15 September 2017.

Version 09.

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All sections	Adoption of the new Medsafe Data Sheet SmPC-style format and content requirements according to NZDS Explanatory Guide, effective 1 March 2017.
Section 4.6 Fertility, pregnancy and lactation	Additional safety information relating to brain development in early life. Pregnancy text updated to reflect doses used in the cited mouse study.
Section 5.1 Description of Clinical Studies/Safety Paediatric	Additional safety information relating to brain development in early life.
Section 5.3 Preclinical Safety Data	Additional safety information relating to brain development in early life.