

AUSTRALIAN PRODUCT INFORMATION

FORTHANE® (ISOFLURANE) ANAESTHETIC INHALATION

1 NAME OF THE MEDICINE

Isoflurane

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Forthane (isoflurane) is a nonflammable general inhalation anaesthetic agent.

Some physical constants are:

Boiling point 760 mm Hg	48.5°C
Refractive index n (20/D)	1.2990 - 1.3005
Specific gravity 25°C	1.496

Vapour pressure in mm Hg*	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 pressures:

$$\log_{10} P_{\text{vap}} = A + \frac{B}{T}$$

A	=	8.056
B	=	-1664.58
T	=	°C + 273.16 (Kelvin)

Partition coefficients at 37°C

water/gas	0.61
blood/gas	1.43
oil/gas	90.8

Partition coefficients at 25°C - rubber & plastic

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

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

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

Age	100% Oxygen	70% N ₂ O
26 ± 4	1.28%	0.56%
44 ± 7	1.15%	0.50%
64 ± 5	1.05%	0.37%

Forthane (isoflurane) is a clear, colourless, stable liquid containing no additives or chemical stabilisers. It has a mildly pungent, musty, ethereal odour. Samples stored in indirect sunlight in clear colourless glass for a five-year period, as well as samples directly exposed for 30 hours to a 2 amp, 115V, 60 cycle long-wave UV light, were unchanged in composition as determined by gas chromatography.

Forthane (isoflurane) does not decompose in the presence of soda lime, and does not attack aluminium, tin, brass, iron or copper.

3 PHARMACEUTICAL FORM

Forthane is a clear colourless liquid for inhalation, containing 100% isoflurane.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Forthane (isoflurane) may be used for induction and maintenance of general anaesthesia. Adequate data have not been developed to establish its use in obstetrical anaesthesia.

4.2 Dose and method of administration

Inspired Concentration

The concentration of Forthane (isoflurane) delivered from a vaporiser during anaesthesia should be known. This may be accomplished by using:

A flow-through type vaporiser specifically calibrated for Forthane (isoflurane).

Vaporisers delivering a saturated vapour which then is diluted (eg. Verni-trol vaporiser). The delivered concentration from a vaporiser of this type may be calculated by using the following formula:

$$\% \text{ Forthane (isoflurane)} = \frac{100 P_V F_V}{F_T (P_A - P_V)}$$

Where:

P_A	=	Atmospheric pressure
P_V	=	Vapor pressure of Forthane (isoflurane)
F_V	=	Flow of gas through vaporiser (mL/minute)
F_T	=	Total flow of gas used (mL/minute)

Forthane (isoflurane) contains no stabiliser. There are no properties of the agent which alter the calibration or the operation of these vaporisers.

Premedication

Premedication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by Forthane (isoflurane) and the heart rate tends to be increased. The use of anticholinergic drugs is a matter of choice.

Induction

Induction with Forthane (isoflurane) in oxygen or in combination with oxygen-nitrous oxide mixtures may produce coughing, breathholding, or laryngospasm. These difficulties may be avoided by the use of a hypnotic dose of an ultra-short-acting barbiturate preceding the Forthane (isoflurane) mixture. Inspired concentrations of 1.5 to 3.0% Forthane (isoflurane) usually produce surgical anaesthesia in 7 to 10 minutes.

Maintenance

Surgical levels of anaesthesia may be sustained with a 1.0-2.5% concentration when nitrous oxide is used concomitantly. An additional 0.5% to 1.0% may be required when Forthane (isoflurane) is given using oxygen alone. If added relaxation is required, supplemental doses of muscle relaxants may be used.

The level of blood pressure during maintenance is an inverse function of Forthane (isoflurane) concentration in the absence of other complicating problems. Excessive decreases may be due to depth of anaesthesia and in such instances should be corrected by decreasing the level of anaesthesia.

As with any potent general anaesthetic, Forthane (isoflurane) should only be administered in an adequately equipped anaesthetising environment by those who are familiar with the pharmacology of the drug and qualified by training and experience to manage the anaesthetised patient.

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 drugs 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.

4.3 Contraindications

Known patient sensitivity to Forthane (isoflurane) or to other halogenated agents and known or suspected genetic susceptibility to malignant hyperthermia.

4.4 Special warnings and precautions for use

Up to concentrations of 1.1 MAC, Forthane (isoflurane) does not increase cerebral blood flow, but will produce increased 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.

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.

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.

Hypotension and respiratory depression increase with increasing depth of anaesthesia.

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.

Malignant Hyperthermia

In susceptible individuals, Forthane (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, tachypnoea, cyanosis, arrhythmias, and unstable blood pressure (It should also be noted that many of these nonspecific signs may appear with light anaesthesia, acute hypoxia, etc.). An increase in overall metabolism may be reflected in an elevated temperature (which may rise rapidly early or late in the case, but usually is not the first sign of augmented metabolism) and an increased usage of the CO₂ absorption system (hot canister). PaO₂ and pH may decrease and hyperkalaemia and a base deficit may appear.

There have been post marketing reports of malignant hyperthermia. Some of these reports have been fatal.

Treatment includes discontinuance of triggering agents (eg. Forthane (isoflurane)), administration of intravenous dantrolene, and application of supportive therapy. Such therapy includes vigorous efforts to reduce body temperature to normal, respiratory and circulatory support as indicated and management of electrolyte fluid balance derangements. (Consult prescribing information for dantrolene sodium intravenous 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.

Use in hepatic impairment

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.

Use in the elderly

No data available.

Paediatric use

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/analgesic/sedation drug administration or other factors such as the surgery or underlying illness.

Published animal studies of some anaesthetic/analgesic/sedation drugs that are NMDA antagonists or GABAergic agonists have reported adverse effects on brain development in early life and late pregnancy (see 5.3 PRECLINICAL SAFETY DATA). The clinical significance of these nonclinical findings is yet to be determined.

With inhalation or infusion of such drugs, exposure is longer than the period of inhalation or infusion. Depending on the drug and patient characteristics, as well as dosage, the elimination phase may be prolonged relative to the period of administration.

Effects on laboratory tests

Transient increases in blood bilirubin, blood glucose and serum creatinine with decreases in BUN, serum cholesterol and alkaline phosphatase have been observed.

4.5 Interactions with other medicines and other forms of interactions

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.

Forthane (isoflurane) is compatible with ancillary drugs normally used in anaesthesia. Forthane (isoflurane) potentiates all commonly used relaxants, the effect being most profound with the non-depolarising type. The M.A.C. (minimum alveolar concentration) is reduced by concomitant administration of N₂O.

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 isoniazide 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

Effects on fertility

No data available.

Use in pregnancy

Category B3.

Forthane (isoflurane) has been shown to have a possible anaesthetic-related embryotoxic and teratogenic effect in mice when given in doses 6 times the expected human dose. The relevance of these studies to the human is not known. There are no adequate well-controlled studies in pregnant women. Hence, Forthane (isoflurane) should not be administered to pregnant women unless clearly needed.

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 judgement 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/analgesic/sedation drugs that are NMDA antagonists or GABAergic agonists have reported adverse effects on brain development in early life and late pregnancy.

Use in lactation

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Forthane (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.

4.8 Adverse effects (Undesirable effects)

Adverse reactions encountered in the administration of Forthane (isoflurane) are in general dose-dependent extensions of pharmacophysiologic effects and include respiratory depression, hypotension and arrhythmias. Potential serious adverse effects include malignant hyperthermia, hyperkalaemia, elevated serum creatine kinase, and myoglobinuria (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Cardiac arrest, bradycardia, and tachycardia have been observed with general inhalation anaesthetic drugs, 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 other general anaesthetic agents, elevations in white blood cell counts lasting up to a few days have been observed even in the absence of surgical stress. Abnormalities of liver function tests, including one case of fulminant hepatic failure, have been observed and jaundice has occurred in a few patients following surgery. Hence the possibility of hepatotoxicity cannot be absolutely excluded.

Rare reports of hypersensitivity (including contact dermatitis, 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 drugs, many of which are known to cause such reactions.

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.

See 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE for information regarding malignant hyperthermia and hepatic injury.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at <http://www.tga.gov.au/reporting-problems>.

4.9 Overdose

In the event of an overdose, or what may appear to be an overdose, stop drug administration, establish a clear airway and initiate assisted or controlled ventilation with 100% oxygen in air.

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 information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Forthane (isoflurane) is a volatile inhalation anaesthetic, indicated for the induction and maintenance of general anaesthesia. It produces a state of unconsciousness, with absence of pain sensation, and provides excellent muscle relaxation. Induction and recovery from Forthane (isoflurane) anaesthesia are rapid. Forthane (isoflurane) has a mild pungency which limits the rate of gaseous induction, although excessive salivation or tracheobronchial secretions do not appear to be stimulated. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anaesthesia may be changed rapidly with Forthane (isoflurane).

Forthane (isoflurane) is a profound respiratory depressant. Respiration must be monitored closely and supported when necessary. As anaesthetic dose is increased, tidal volume decreases and respiratory rate is unchanged. This depression is partially reversed by surgical stimulation, even at deeper levels of anaesthesia.

With controlled ventilation and normal Pa CO₂, cardiac output is maintained, despite increasing depth of anaesthesia, primarily through an increase in heart rate which compensates for a reduction in stroke volume. The hypercapnia which attends spontaneous ventilation during Forthane (isoflurane) anaesthesia further increases heart rate and raises cardiac output above awake levels. Forthane (isoflurane) evokes a sigh response.

There is a decrease in blood pressure during induction of anaesthesia due to peripheral vasodilation, but this returns to near normal values with surgical stimulation. Progressive

increases in depth of anaesthesia produce corresponding decreases in blood pressure. Nitrous oxide diminishes the inspiratory concentration of Forthane (isoflurane) required to reach a desired level of anaesthesia and may reduce the arterial hypotension seen with Forthane (isoflurane) alone. Cardiac rhythm is remarkably stable.

Forthane (isoflurane) does not sensitise the myocardium to exogenously administered adrenaline in the dog. Limited data indicate that subcutaneous injection of 0.25mg of adrenaline (50mL of 1:100,000 solution) does not produce an increase in ventricular arrhythmias in patients anaesthetised with Forthane (isoflurane).

Muscle relaxation often is adequate for intra-abdominal operations at maintenance levels of anaesthesia. Complete muscle paralysis can be attained with small doses of muscle relaxants. All commonly used muscle relaxants are markedly potentiated with Forthane (isoflurane), the effect being most profound with the non-depolarising type. Neostigmine reverses the effect of non-depolarising muscle relaxants in the presence of Forthane (isoflurane). All commonly used muscle relaxants are compatible with Forthane (isoflurane).

Clinical trials

No data available.

5.2 Pharmacokinetic properties

Metabolism

Forthane (isoflurane) is only minimally metabolised, much less than any other halogen containing agent currently used in anaesthesia. The average recovery in exhaled air is 95% (SE 7%). The post-operative increase of urinary excretion of fluoride and organic fluoride accounted for less than 0.2% of fluorine administered as Forthane (isoflurane). The principal metabolite detected in the urine is the non-ionic fluoride, trifluoroacetic acid. The uptake and excretion of Forthane (isoflurane) are found to be consistent with its measured blood-gas coefficient of 1.4. Forthane (isoflurane) anaesthetised patients in one study showed a mean serum inorganic fluoride level of 4.4 micromole/L. These levels are well below the threshold level which can produce minimal renal toxicity (40 micromole/L). Other studies in rats, mice and guinea pigs with repeated exposure to anaesthetic levels of the agent, suggest that Forthane (isoflurane) is less toxic than other halogenated anaesthetics.

5.3 Preclinical safety data

Animal studies based on blood chemistry measurements showed that no significant short or long term changes were produced by Forthane (isoflurane) anaesthesia. No toxic effect

occurred after the administration to humans of anaesthesia-inducing doses of Forthane (isoflurane) other than slight leukocytosis as with other anaesthetics. It is concluded that Forthane (isoflurane) is an effective anaesthetic and produces no biochemical or physiological changes which are substantially different from those produced by established volatile anaesthetic agents.

Published studies in pregnant and juvenile animals suggest that the use of anaesthetic/analgesic 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.

Teratology

Reproductive and teratogenic effects of Forthane (isoflurane) were studied in Swiss-Webster mice exposed for 4 hours per day, on days 6-15 of pregnancy, to 0.006%, 0.06% or 0.6% isoflurane, using compressed air as the carrier gas. There were no differences among groups in litter size or sex ratio, but significant morphological abnormalities occurred in the 0.6% isoflurane group. Foetuses of the mice exposed to this highest dose of isoflurane demonstrated an increased incidence of cleft palate, reduced skeletal ossification, minor hydronephrosis and increased renal pelvic cavitation. Exposure of Swiss-Webster mice to 0.006% and 0.06% isoflurane concentrations did not adversely affect reproductive indices and foetal development. Only exposure that resulted in light general anaesthesia (0.6%) was associated with foetotoxic effects. Most of these effects (ie. decreased birth weight, reduced ossification, minor hydronephrosis, and increased renal pelvic cavitation) are indicative of retarded foetal maturation and do not result in permanent abnormalities or in decreased survival, and similar effects have been observed with the other volatile agents. However the incidence of cleft palate is significantly higher in the isoflurane group. These results are from one rodent strain and extrapolation to humans must be done with caution. There are no adequate well-controlled studies in pregnant women. The data suggest that should a pregnant woman require an anaesthetic, particularly during the period of organogenesis, isoflurane should not be administered unless clearly needed.

Genotoxicity

No data available.

Carcinogenicity

Swiss ICR mice were given Forthane (isoflurane) to determine whether such exposure might induce neoplasia. Forthane (isoflurane) was given at 1/2, 1/8 and 1/32 MAC for four in-utero exposures and for 24 exposures to the pups during the first nine weeks of life. The mice were killed at 15 months of age. The incidence of tumours in these mice was the same as in untreated control mice which were given the same background gases, but not the anaesthetic.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Forthane comprises 100% of the active substance Isoflurane. There are no excipients in this drug product formulation.

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine. Refer to Section 2 QUALITATIVE AND QUANTITATIVE COMPOSITION for information on partition coefficients applicable to specific rubber and plastics.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30°C. Keep bottle tightly closed.

6.5 Nature and contents of container

Forthane (isoflurane) is packaged in 100mL* and 250mL amber glass bottles.

*Note: 100mL size is not currently marketed

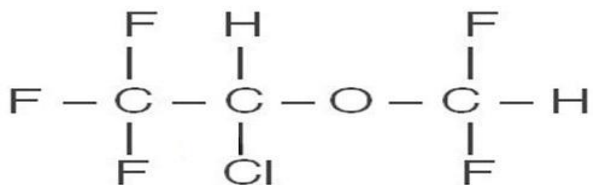
6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Chemical structure

It is 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether, and its structural formula is:



CAS number

26675-46-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4. Prescription only medicine.

8 SPONSOR

AbbVie Pty Ltd
241 O'Riordan Street
Mascot NSW 2020
Australia

9 DATE OF FIRST APPROVAL

21 October 1991

10 DATE OF REVISION

24 October 2018

Summary table of changes

Section Changed	Summary of new information
All sections	Reformat to align with revised TGA PI requirements
4.4, 4.6 and 5.3	Safety update to include information regarding published studies of anaesthetic/sedation drugs showing adverse effects on brain development in early life and late pregnancy.