PRODUCT INFORMATION

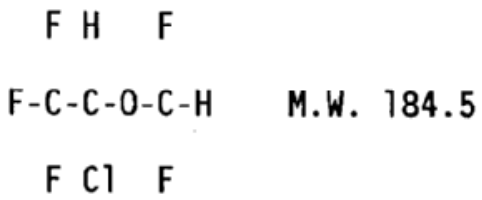
FORTHANE®

NAME OF THE MEDICINE

Isoflurane

Chemical Structure

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



CAS Number

26675-46-7

DESCRIPTION

Forthane (isoflurane) is a nonflammable general inhalation anaesthetic agent.
Some physical constants are:

Boiling point 760 mm Hg		48.5ºC
Refractive index n $\frac{20}{D}$		1.2990 - 1.3005
Specific gravity 25ºC		1.496
Vapour pressure in mm Hg*	18ºC	218
	20ºC	238
	22ºC	261
	24ºC	285
	25ºC	295
	26ºC	311
	30ºC	367
	35ºC	450

* Equation for vapour pressures:

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

A = 8.056

B = -1664.58

T = ºC + 273.16 (Kelvin)

Partition coefficients at 37ºC

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

Partition coefficients at 25ºC - 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 & 23ºC None

Lower limit of flammability in oxygen or nitrous oxide at 900 joules/sec & 23ºC Greater than useful concentration in anaesthesia

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

Age	100% Oxygen	70% N_{2O}
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. Forthane (isoflurane) 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.

PHARMACOLOGY

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 CO_2, 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 arrhthmias 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 nondepolarising type. Neostigmine reverses the effect of nondepolarising muscle relaxants in the presence of Forthane (isoflurane). All commonly used muscle relaxants are compatible with Forthane (isoflurane).

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, trifluoracetic 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 4.4µM/L. These levels are well below the threshold level which can produce minimal renal toxicity (40µM/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.

Toxicology

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.

* Carcinogenicity

  Carcinogenesis: 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.

* 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.

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.

CONTRAINDICATIONS

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

PRECAUTIONS

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.

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.

Replacement of Desiccated CO_2 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 CO_2 absorbents, specifically those containing potassium hydroxide (e.g., Baralyme). When a clinician suspects that the CO_2 absorbent may be desiccated, it should be replaced before the administration of isoflurane. The colour indicator of most CO_2 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. CO_2 absorbents should be replaced routinely regardless of the state of the colour indicator.

General: 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.

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.

Information to Patients: Forthane (isoflurane), as well as other general anaesthetics, may cause a slight decrease in intellectual function for 2 to 4 days following anaesthesia. As with other anaesthetics, small changes in moods and symptoms may persist for up to 6 days after administration (See **Effects on Ability to Drive and Use Machines**).

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, tachcardia, tachypnea, cyanosis, arrythmias, 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 CO_2 absorption system (hot canister). PaO_2 and pH may decrease and hyperkalaemia 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 [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 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.

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.

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 **PRECAUTIONS**).

Effect 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.

Interactions with other Medicines

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 nondepolarising type. The M.A.C. (minimum alveolar concentration) is reduced by concomitant administration of N_2O.

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.

Inducers of CYP2E1: 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 derivates.

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.

ADVERSE 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 arrythmias. Potential serious adverse effects include malignant hyperthermia, hyperkalaemia, elevated serum creatine kinase, and myoglobinuria (see **PRECAUTIONS**).

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 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 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 **PRECAUTIONS** for information regarding malignant hyperthermia and hepatic injury.

DOSAGE & 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 bartibuate 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.

OVERDOSAGE

In the event of overdosage, or what may appear to be overdosage, 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.

PRESENTATION AND STORAGE CONDITIONS

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

Storage: Store below 30ºC. Keep bottle tightly closed. Shelf life 5 years.

NAME AND ADDRESS OF THE SPONSOR

Made in UK for:

ABBVIE PTY LTD
241 O'Riordan Street
Mascot NSW 2020
Australia

POISON SCHEDULE OF THE MEDICINE

Schedule 4

DATE OF FIRST INCLUSION IN THE ARTG

21 October 1991

DATE OF MOST RECENT AMENDMENT

9 December 2014