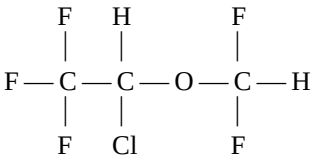
FORANE
TECHNICAL LEAFLET

Composition and Description
Isoflurane (not less than 99.9% w/w)

Forane is a non flammable inhalational liquid, administered by inhalation of the vapour. It is 1-chloro-2,2,2,-trifluoroethyl difluoromethyl ether and its structural formula is:



Some physical constants of Forane are:

Molecular weight	184.5
Boiling point at 760 mm Hg	48.5^{o}C
Refractive index n^{20}_{D}	1.2990-1.3005
Specific gravity at 25^{o}C	1.496

Vapour pressure, mm Hg

at 20^{o}C	238
at 25^{o}C	295
at 30^{o}C	367
at 35^{o}C	450

Partition coefficients at 37^{o}C:

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

Partition coefficients at 25^{o}C for rubber and plastics:

Conductive rubber/gas	62.0
Butyl rubber/gas	75.0
Polyvinyl chloride/gas	110.0
Polyethylene/gas	ca2.0
Polyurethane/gas	ca1.4
Polyolefin/gas	ca1.1
Butyl acetate/gas	ca2.5

Purity by gas chromatography: better than 99.9%

Flammability in oxygen or nitrous oxide:

at 9 joules/sec. and 23^{o}C non flammable

at 900 joules/sec. and 23^{o}C non flammable at anaesthetic concentrations.

The table below indicates average MAC values for different age groups

ADULTS		
Age	**Average MAC Value in 100 % Oxygen**	**70% N_2O**
26 ± 4 years	1.28%	0.56%
44 ± 7 years	1.15%	0.50%
64 ± 5 years	1.05%	0.37%
PAEDIATRIC POPULATION		
Age	**Average MAC Value in 100% Oxygen**	
Preterm neonates < 32 weeks gestational age	1.28%	
Preterm neonates 32-37 weeks gestational age	1.41%	
0-1 month	1.60%	
1-6 months	1.87%	
6-12 months	1.80%	
1-5 years	1.60%	

Forane is a stable, colourless liquid, with no added chemical stabiliser.

Forane has a slightly pungent, musty odour. No change in the composition of samples exposed for 5 years to indirect sunlight in clear colourless bottles, nor in that of samples exposed for 30 hours to UV light was detectable by gas chromatography.

There was no consumption of alkali when Forane was exposed for more than 6 months to a 1 N sodium methoxide in methanol solution, demonstrating high stability to strong base. Forane does not decompose in the presence of soda lime and does not attack aluminium, tin, brass, copper or iron.

Actions

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 change rapidly with Forane. Heart rhythm remains stable.

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

Hypotension and myocardial depression are related to the depth of anaesthesia. The concomitant use of nitrous oxide and surgical stimulation may limit the extent of the hypotension. Excessive fall in blood pressure, unless due to hypovolaemia, should be corrected by lightening depth of anaesthesia.

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

Electroencephalographic changes and convulsions are extremely rare with Forane.

Forane 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 Forane.

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. All commonly used muscle relaxants are markedly potentiated by Forane, 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 Forane itself. All commonly used muscle relaxants are compatible with Forane.

Forane may be used for the induction and maintenance of general anaesthesia.

Forane undergoes minimal biotransformation in man. In the post-operative period only 0.17% of the Forane taken up can be recovered as urinary metabolites. Peak serum inorganic fluoride values usually average less than 5 μmol/litre and occur about four hours after anaesthesia, returning to normal levels within 24 hours. No signs of renal injury have been reported after Forane administration.

Preclinical safety data

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 is not known.

Dosage and Administration

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

Overall, MAC values for Forane diminish with age. The table above indicates average MAC values for different age groups.

Premedication: drugs used for premedication should be selected for the individual patient, bearing in mind the respiratory depressant effect of Forane. The use of anticholinergic drugs is a matter of choice, but may be advisable for inhalation induction in paediatrics.

Induction: To avoid excitement an intravenous induction agent should be administered followed by inhalation of Forane. Forane with oxygen or with an oxygen/nitrous oxide mixture may be used.

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

Induction of anaesthesia in children:

Isoflurane is not recommended for use as an inhalation induction agent in infants and children because of the occurrence of cough, breath-holding, desaturation, increased secretions and laryngospasm (see Precautions).

Maintenance: surgical levels of anaesthesia may be maintained with 1.0 - 2.5% Forane in oxygen/nitrous oxide mixtures. An additional 0.5-1.0% Forane may be required when given with oxygen alone. For caesarian section, 0.5-0.75% Forane in a mixture of oxygen/nitrous oxide is suitable.

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

Elderly: as with other agents, lesser concentrations of Forane are normally required to maintain surgical anaesthesia in elderly patients. See above for MAC values.

Contra-indications, Warnings, etc.
Use in patients in whom liver dysfunction, jaundice or unexplained fever, leucocytosis or eosinophilia has occurred after a previous halogenated anaesthetic administration. Forane is contraindicated in patients with known sensitivity to Forane or other halogenated anaesthetics. It is also contraindicated in patients with known or suspected genetic susceptibility to malignant hyperthermia and in all patients (adults and children) undergoing dental procedures outside a hospital or day care unit (see Precautions).

Rare cases of extreme heat, smoke and/or spontaneous fire in the anaesthesia machine have been reported during the 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 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.

Precautions:
Vaporisers specially calibrated for Forane should be used so that the concentration of anaesthetic delivered can be accurately controlled. Hypotension and respiratory depression increase as anaesthesia is deepened.

Increased blood losses comparable with those found following anaesthesia with other inhalation agents have been recorded with isoflurane in patients undergoing uterine curettage. Isoflurane, like other inhalational agents, has relaxant effects on the uterus with the potential risk for uterine bleeding. Clinical judgment should be exercised when using isoflurane during obstetric anaesthesia. Consideration should be taken to use the lowest possible concentration of isoflurane in obstetrical operations (see Use in pregnancy).

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. (Please see Undesirable Effects).

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

As with any potent general anaesthetic, Forane 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.

Since levels of anaesthesia may be altered quickly and easily with Forane, 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 in 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. Cirrhosis, viral hepatitis or other preexisting liver disease can be a reason to select an anaesthetic other than a halogenated anaesthetic.

All patients anaesthetised with Forane should be constantly monitored, including ECG, BP, oxygen saturation and end tidal CO_2, in a setting where full resuscitative equipment is available and with staff fully trained in resuscitative techniques. The presence of additional risk factors should be taken into consideration (see Undesirable Effects)
Isoflurane markedly increases cerebral blood flow at deeper levels of anaesthesia. There may be a transient rise in cerebral spinal fluid pressure which is reversible with hyperventilation. Isoflurane must be used with caution in patients with increased intracranial pressure. In such cases hyperventilation may be necessary. This should be borne in mind when considering for use in neurosurgery.

Use of isoflurane in hypovolemic, hypotensive and debilitated patients has not been extensively investigated. A lower concentration of isoflurane is recommended for use in these patients.

All commonly used muscle relaxants are markedly potentiated by isoflurane, the effect being most profound with non-depolarising agents.

Isoflurane may cause a slight decrease in intellectual function for 2-4 days following anaesthesia. Small changes in moods and symptoms may persist for up to 6 days after administration. This must be taken into account when patients resume normal daily activities, including driving or operating heavy machinery.

A potentiation of neuromuscular fatigue can be seen in patients with neuromuscular diseases, such as myasthenia gravis. Forane should be used with caution in these patients.

Forane should be administered with caution to patients who can develop bronchoconstriction since bronchospasm can occur (see Undesirable Effects).

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 (see Undesirable Effects).
Measurement of tidal volume may provide an indication of depth of anaesthesia in the spontaneously breathing patient.

During the induction of anaesthesia, saliva flow and tracheobronchial secretion can increase and can be the cause of laryngospasm, particularly in children (see Undesirable Effects).

Children Under Two Years of Age: Caution should be exercised when Forane is used in small children due to limited experience with this patient-group.

Malignant hyperthermia: In susceptible individuals, Forane (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 non-specific features such as muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and unstable blood pressures. (It should also be noted that many of these non-specific signs may appear with light anaesthesia, acute hypoxia, etc.) PaO_2 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. Forane). 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 dantrolene sodium intravenous for additional information on patient management). Renal failure may appear later and urine flow should be sustained if possible.

Perioperative Hyperkalemia
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 consistant with myoglobinuria. Despite the similarity in presentation to malignant hyperthermia, none of these patients exhibited signs or symptoms of muscle rigidity of hypermetabolic state. Early and aggressive intervention to treat the hyperkalaemia and resistant arrhythmias is recommended, as is subsequent evaluation for latent neuromuscular disease.

Although peak inorganic fluoride concentrations which result from the breakdown of isoflurane are generally much lower than those considered nephrotoxic, no information is available on levels in patients with compromised renal function. The drug should therefore be used with extreme caution in these patients, or in those receiving nephrotoxic drugs concomitantly.

Caution should also be employed when administering Forane to those receiving antihypertensive or other drugs which may influence the sympathetic nervous system.

There is insufficient experience of use in repeated anaesthesia to make a definite recommendation in this regard. As with all halogenated anaesthetics, repeat anaesthesia within a short period of time should be approached with caution.

Isolated cases of increased carboxyhemoglobin 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 CO_2 absorbents.

Standard anaesthesia monitors such as pulse oximeters are not a reliable method for detecting carboxyhaemoglobin. Direct measurement of carboxyhaemoglobin should be carried out in the event that a patient on closed circuit anaesthesia with an implicated agent develops oxygen desaturation which does not respond to the usual therapeutic measures.

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

Interactions:
Combinations advised against:

Concomitant use of succinylcholine with inhaled anesthetic agents has been associated with rare increase in serum potassium levels that have resulted in cardiac arrhythmias and death in paediatric patients during the post-operative period.

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. Treatment should be stopped 15 days prior to surgery.

Combinations requiring precautions in using:

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.

Indirect-acting sympathomimetics (amphetamines and their derivatives, psychostimulants, appetite suppressants, ephedrine and its derivatives): Risk of perioperative hypertension. In patients undergoing elective surgery, treatment should ideally be discontinued several days before surgery.

Adrenaline, by subcutaneous or gingival injections: risk of serious ventricular arrhythmia as a consequence of increased heart rate, although the myocardial sensitivity with respect to adrenaline is lower with the use of isoflurane than in the case of halothane.

Cardiovascular compensation reactions may be impaired by beta-blockers.

Use of isoflurane and isoniazide can increase the risk of potentiation of the hepatotoxic effects.

Calcium antagonists, in particular dihydropyridine derivates: isoflurane may lead to marked hypotension in patients treated with calcium antagonists.

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, and caution should be exercised when concomitantly administered with isoflurane.

All commonly used muscle relaxants are markedly potentiated by isoflurane, the effect being most profound with non-depolarising agents.Neostigmine has an effect on the nondepolarising relaxants, but has no effect on the relaxing action of isoflurane itself. Care should also be exercised when using antibiotics of the aminoglycoside group e.g. neomycin, concurrently with isoflurane.

Isoflurane does not sensitise the myocardium to the effects of catecholamines in dogs. Limited data suggests that subcutaneous infiltration of 0.25 mg (50 ml of 1:200,000 solution) adrenaline of 3.4 mcg/kg in a 70 kg adult, does not produce an increase in ventricular arrhythmias, provided there is no concomitant myocardial hypoxia. The utmost care must be used to prevent overdosage or unduly rapid adrenaline absorption.

MAC (minimum alveolar concentration) is reduced by concomitant administration of N20 in adults.

Use in Pregnancy: There are no or limited amount of data from the use of isoflurane in pregnant women. Studies in animals have shown reproductive toxicity. 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 exercised when using isoflurane during obstetric anaesthesia. Consideration should be taken to use the lowest possible concentration of isoflurane in obstetrical operations.

Studies in animals have shown reproductive toxicity (see section **Actions**).

Use in Cesarean Section:
Isoflurane, in concentrations up to 0.75%, has been shown to be safe for the maintenance of anaesthesia for cesarean section (please see Precautions).

Nursing Mothers*:* It is not known whether isoflurane/metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when isoflurane is administered to a nursing woman.

Undesirable Effects

a. Summary of the safety profile

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, anaphylactic reactions, liver adverse reactions, hyperkalemia, elevated serum creatine kinase and myoglobinuria (please see Precautions and Undesirable Effects). Shivering, nausea, vomiting, ileus, agitation and delirium have been observed in the postoperative period.

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

b. Tabulated summary of adverse reactions

The following table displays adverse reactions reported in clinical trials and from post-marketing experience. Frequency cannot be estimated from the available data, therefore it is "unknown".

Summary of Most Frequent Adverse Drug Reactions		
SOC	**Frequency**	**Adverse Reactions**
Blood and lymphatic system disorders	Unknown	Carboxyhaemoglobinaemia[2]
Immune system disorders	Unknown	Anaphylactic reaction[1]
	Unknown	Hypersensitivity[1]
Metabolsim and nutrition disorders	Unknown	Hyperkalaemia[2]
	Unknown	Blood glucose increased[1]
Psychiatric disorders	Unknown	Agitation
	Unknown	Delirium
	Unknown	Mood altered[5]
Nervous system disorders	Unknown	Convulsion
	Unknown	Mental impairment[4]
Cardiac disorders	Unknown	Arrhythmia
	Unknown	Cardiac arrest
	Unknown	Bradycardia
	Unknown	Tachycardia
	Unknown	Electrocardiogram QT prolonged[1]
	Unknown	Torsade de pointes[1]
Vascular disorders	Unknown	Hypotension[2]
	Unknown	Haemorrhage[3]
Respiratory, thoracic and mediastinal disorders	Unknown	Bronchospasm[1],[2]
	Unknown	Dyspnoea[1]
	Unknown	Wheezing[1]
	Unknown	Respiratory depression[2]
	Unknown	Laryngospasm[1],[2]
Gastrointestinal disorders	Unknown	Ileus
	Unknown	Vomiting
	Unknown	Nausea
Hepatobiliary disorders	Unknown	Hepatic necrosis[2]
	Unknown	Hepatocellular injury[2]
	Unknown	Blood bilirubin increased[1]
Skin and subcutaneous tissue disorders	Unknown	Swelling face[1]
	Unknown	Dermatitis contact[1]
	Unknown	Rash[1]
Renal and urinary disorders	Unknown	Blood creatinine increased[1]
	Unknown	Blood urea decreased
General disorders and	Unknown	Hyperthermia malignant[2]

administration site conditions	Unknown	Chest discomfort[1]
	Unknown	Chills
Investigations	Unknown	White blood cell count increased[1]
	Unknown	Hepatic enzyme increased[2]
	Unknown	Fluoride increased[1]
	Unknown	Electroencephalogram abnormal
	Unknown	Blood cholesterol decreased[1]
	Unknown	Blood alkaline phosphatase decreased[1]
Musculoskeletal and connective tissue disorders	Unknown	Myoglobinuria
	Unknown	Rhabdomyolysis

[1]See Undesirable Effects(c)
[2]See Precautions
[3]Isoflurane, like other inhalational agents, has relaxant effects on the uterus with the potential risk for uterine bleeding. See Precautions
[4]May cause a slight decrease in intellectual function for 2-4 days after anaesthesia. See Precautions.
[5]Small changes in moods and symptoms may persist for up to 6 days. See Precautions.

c. Description of selected adverse reactions

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 etiology 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 (mean 4.4 µmol/l in one study) could cause renal toxicity, as these are well below the proposed threshold levels for kidney toxicity.

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

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

d. 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 postoperative period. (See Precautions.)

During the induction of anaesthesia, saliva flow and tracheobronchial secretion can increase and can be the cause of laryngospasm. (See Precautions)

e. 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 postoperative 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 Precautions)

Elderly:
Lesser concentrations of isoflurane are normally required to maintain surgical anaesthesia in elderly patients. (See Dosage and Administration)

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 via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

Pharmaceutical Precautions

Do not store above 25°C. Store in the original package in order to protect from light. Keep the bottle tightly closed. Keep out of the sight and reach of children. In-use stability: Use within 3 months from opening when stored in the original package and below 25°C.

Package Information

Forane is supplied in Type III Ph.Eur., amber glass bottles of (100ml and 250 mle), closed with an aluminium cap with LDPE liner. Not all pack sizes may be marketed.

Further Information

Nil

Product Authorisation Number

PA 1824/1/1

AbbVie Limited
Citywest Business Campus
Dublin 24
Ireland

Date of Approval

Month YYYY