

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Forane 99.9% w/w, Inhalation Vapour, Liquid

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Isoflurane (not less than 99.9% w/w).

3 PHARMACEUTICAL FORM

Inhalation Vapour, Liquid.

Clear colourless liquid with slightly musty odour for vaporisation and administration as an inhalation gas.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Induction and maintenance of general anaesthesia in adults and children. Use of isoflurane in dental anaesthesia should be restricted to hospitals or day care units only (see section 4.3).

4.2 Posology and method of administration

Posology

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 below indicates average MAC values for different age groups.

ADULTS		
Age	Average MAC Value in 100 % Oxygen	70% N₂O
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%	

Method of administration

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 section 4.4).

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.

Older patients:

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

4.3 Contraindications

Use in patients in whom liver dysfunction, jaundice or unexplained fever, leucocytosis or eosinophilia has occurred after a previous halogenated anaesthetic administration.

Forane is contra-indicated 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.

Forane is contraindicated in all patients (adults and children) undergoing dental procedures outside a hospital or day care unit (see section 4.4).

4.4 Special warnings and precautions for use

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 section 4.6).

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. (see section 4.8).

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

disorders.

General

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 CO₂ 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 section 4.8).

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 the 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.

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 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 (see to section 4.7).

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 section 4.8).

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 section 4.8). 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 thracheobronchial secretion can increase and can be the cause of laryngospasm, particularly in children (see section 4.8).

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.) 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. 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 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.

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.

This agent should be administered cautiously to those on anti hypertensives or any drug which may influence the response of the sympathetic nervous system.

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 CO₂ 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.

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 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 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.

4.5 Interaction with other medicinal products and other forms of interaction

Combinations advised against:

Concomitant use of succinylcholine with inhaled anesthetic 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.

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:

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.

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

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.

Calcium antagonists, in particular dihydropyridine derivatives: 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 N2O in adults (see section 4.2).

4.6 Fertility, pregnancy and lactation

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.

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 refer to section 4.4).

Breast-feeding

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.

4.7 Effects on ability to drive and use machines

Isoflurane can have an influence on driving and using machines. The patient should not drive or use machines for 2-4 days following anaesthesia with isoflurane. Changes in behaviour and intellectual function 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.

4.8 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 (see sections 4.4 and 4.8). 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
Metabolism 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 administration site conditions	Unknown	Hyperthermia malignant ²
	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

¹See 4.8(c)²See 4.4³ Isoflurane, like other inhalational agents, has relaxant effects on the uterus with the potential risk for uterine bleeding. See 4.4.⁴May cause a slight decrease in intellectual function for 2-4 days after anaesthesia. See 4.4.⁵Small changes in moods and symptoms may persist for up to 6 days. See 4.4.**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 $\mu\text{mol/l}$ 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 section 4.4.)

During the induction of anaesthesia, saliva flow and tracheobronchial secretion can increase and can be the cause of laryngospasm. (see section 4.4.)

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 section 4.4.)

Elderly:

Lesser concentrations of isoflurane are normally required to maintain surgical anaesthesia in elderly patients. (see section 4.2.)

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.

4.9 Overdose

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: N01AB06 Halogenated hydrocarbon.

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.

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 (See also Section 4.5).

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 (see also Section 4.5).

5.2 Pharmacokinetic properties

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.

5.3 Preclinical safety data

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

Some halogenated inhalation agents with a CH-F₂ moiety, i.e. desflurane, isoflurane and enflurane have been reported to interact with dry CO₂ absorbents to form carbon monoxide. In order to minimise the risk of formation of carbon monoxide in closed and re-breathing circuits, and the possibility of increased carboxyhaemoglobin levels in exposed patients, CO₂ absorbents should not be allowed to dry out (see also section 4.4).

6.3 Shelf life

5 years.

In-use stability: Use within 3 months from opening when stored in the original package and below 25°C.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package in order to protect from light. Keep the bottle tightly closed.

6.5 Nature and contents of container

100 ml and 250 ml Type III Ph.Eur. amber glass bottles, closed with an aluminium cap with LDPE liner.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Vaporisers specially calibrated for Forane 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 MARKETING AUTHORISATION HOLDER

AbbVie Limited
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1824/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23rd June 1983

Date of last renewal: 23rd June 2008

10 DATE OF REVISION OF THE TEXT

January 2016