

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

AErrane (isoflurane), 100% v/v inhalation vapour, liquid

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Isoflurane 100% v/v.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Inhalation vapour, liquid
Clear, colourless liquid.

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 Contraindications, Section 4.3).

4.2 Posology and method of administration

In order to be able to accurately control the precise concentration of isoflurane, vaporisers that have been specially calibrated for isoflurane should be used.

To avoid excitement and because of the irritant effects on the respiratory tract, an intravenous induction agent should be administered, followed by inhalation of isoflurane.

Induction should be initiated at 0.5%. Concentrations of 1.5 - 3.0% in O₂ or O₂/N₂O usually produce surgical anaesthesia in 7 -10 minutes.

The usual concentration is 1 - 2.5% in O₂/N₂O or 1.5 – 3.5% with O₂ alone.

For Caesarean section, 0.5 - 0.75% in a mixture of O₂/N₂O is suitable.

Recovery

The concentration of AErrane must be reduced to 0.5% at the end of the operation, or to 0% during closure of the wound to allow prompt recovery.

If all administration of anaesthetic agents has been stopped, the air passages of the patient should be ventilated several times with 100% oxygen until complete awakening occurs.

If the vector gas is a mixture of 50% O₂ and 50% N₂O, the value of the minimum alveolar concentration of isoflurane is approximately 0.65%.

ADULTS		
Age	Average MAC Value in 100% Oxygen	70% N ₂ O
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%	

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

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).

4.3 Contraindications

- Isoflurane is contraindicated in patients with known sensitivity to isoflurane or other halogenated anaesthetics.
- It is also contraindicated in patients with known or suspected genetic susceptibility to malignant hyperthermia.
- Patients in whom liver dysfunction, jaundice or unexplained fever, leucocytosis, or eosinophilia has occurred after a previous halogenated anaesthetic administration.
- 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

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

Vaporizers specially calibrated for isoflurane should be used so that the concentration of anesthetic delivered can be accurately controlled. Hypotension and respiratory depression increase as anaesthesia is deepened. The extent of blood pressure reduction and respiratory depression can be an indication of the extent of anaesthesia. Spontaneous respiration must be carefully monitored and must be assisted if necessary. All patients anaesthetised with isoflurane 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 also Section 4.8).

Since levels of anaesthesia may be altered quickly and easily with isoflurane, only vaporisers which deliver a predictable output with reasonable accuracy, or techniques during which inspired or expired concentrations can be monitored, should be used. The degree of hypotension and respiratory depression may provide some indication of anaesthetic depth.

Reports 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 anesthesia, including isoflurane, to patients with mitochondrial disorders.

Increased blood losses comparable with those found following anaesthesia with other inhalation agents have been recorded with Isoflurane in patients undergoing gynaecological surgical procedures involving uterine curettage.

With the use of halogenated anaesthetics, disruption of the liver function, icterus, and fatal liver necrosis have been reported. Such reactions appear to indicate hypersensitivity reactions to anaesthetics. 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. Cirrhosis, viral hepatitis or other preexisting liver disease can be a reason to select an anaesthetic other than a halogenated anaesthetic.

Isoflurane is a profound respiratory depressant whose effect is accentuated by narcotic premedication or concurrent use of other respiratory depressants. Respiration should be closely monitored, and assisted or controlled ventilation employed when necessary (See section 4.8).

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.

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

It is recommended that ventilation be controlled in neurosurgery patients: cerebral blood flow remains unchanged in the course of light anaesthesia. Isoflurane markedly increases cerebral blood flow at deeper levels of anaesthesia. There may be a transient rise in cerebral spinal fluid pressure. In most cases, this pressure increase can be prevented by hyperventilation.

Isoflurane must be used with caution in patients with increased intracranial pressure. In such cases hyperventilation may be necessary

Isoflurane should be administered with caution to patients who can develop bronchoconstriction since bronchospasm can occur (see section 4.8).

Regardless of the anaesthetics employed, maintenance of normal hemodynamics is important to the avoidance of myocardial ischemia in patients with coronary artery disease. Isoflurane can produce a coronary vasodilation at the arteriolar level in selected animal models; the drug is probably also a coronary dilator in humans. Isoflurane, like some other coronary arteriolar dilators, has been shown to divert blood from collateral dependent myocardium to normally perfused areas in an animal model ("coronary steal"). Clinical studies to date evaluating myocardial ischaemia, infarction and death as outcome parameters have not established that the coronary arteriolar dilation property of isoflurane is associated with coronary steal or myocardial ischaemia in patients with coronary artery disease.

In light of the fact that Isoflurane acts in an irritating manner on the mucous membranes, the product is difficult to use if inhalation anaesthesia is applied via mask.

During the induction of anaesthesia, saliva flow and tracheobronchial secretion can increase and can be the cause of laryngospasm, particularly in children (see section 4.8).

A transient increase in bromsulphthalein retention, blood glucose, and serum creatinine with a decrease in the serum urea level, serum cholesterol level, and alkaline phosphatase level, has been observed following administration of isoflurane.

Malignant Hyperthermia

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

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 hyperkalemia and a base deficit may appear. Fatal outcome of malignant hyperthermia has been reported with isoflurane. Treatment includes discontinuance of triggering agents (e.g. isoflurane), intravenous administration of dantrolene sodium, and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support as indicated, and management of electrolyte-fluid-acid-base derangements. (Consult prescribing information for dantrolene sodium intravenous for additional information on patient management.) Renal failure may appear later.

Isolated cases of increased carboxyhemoglobin have been reported with the use of halogenated inhalation agents with a -CF₂H moiety (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.

As with other halogenated anaesthetics, isoflurane has been reported to interact with dry carbon dioxide adsorbents during closed circuit anaesthesia, to form carbon monoxide. Inhalation of carbon monoxide may lead to formation of significant levels of carboxyhaemoglobin in exposed patients. In the event that a patient on closed circuit anaesthesia using isoflurane develops oxygen desaturation, which does not respond to the usual therapeutic corrective measures, direct measurement of carboxyhaemoglobin should be carried out. Note that pulse oximetry is not a reliable method for detecting carboxyhaemoglobin. All necessary precautions should be taken to insure that carbon dioxide adsorbents are not allowed to dry out.

Perioperative Hyperkalaemia:

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 of isoflurane in hypovolaemic, hypotensive and debilitated patients has not been extensively investigated. As with other potent inhaled anaesthetics, a lower concentration is recommended for use in these patients.

Isoflurane must always be used with caution in patients with untreated decompensation of cardiocirculatory function, and only after careful consideration of the risks and benefits based on the patient's clinical situation.

Use of inhaled anaesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in pediatric 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 hyperkalemia and resistant arrhythmias is recommended, as is subsequent evaluation for latent neuromuscular disease.

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 administration of isoflurane. The color indicator of most CO₂ absorbents does not necessarily change as a result of desiccation. Therefore, the lack of significant color 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.

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 (please refer to section 4.7).

Isoflurane relaxes the uterus muscle, and the lowest possible concentration of isoflurane should be used in obstetrical operations (Please refer to section 4.6).

All commonly used muscle relaxants are markedly potentiated by Isoflurane, the effect being most profound with non-depolarizing agents. (Please refer to section 4.5)

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

4.5 Interaction with other medicinal products and other forms of interaction

The simultaneous administration of isoflurane and the following products requires strict supervision of the condition of the patient;

Combinations advised against:

- 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 and hemodynamic instability during surgery or medical procedures. Treatment should be stopped 15 days prior to surgery.

Combinations requiring precautions in using:

- Beta-blockers: Concomitant use of beta blockers may exaggerate the cardiovascular effects of inhalational anesthetics, including hypotension and negative inotropic effects. Cardiovascular compensation reactions may be impaired by beta-blockers.
- Use of Isoflurane and isoniazide can increase the risk of potentiation of the hepatotoxic effects.
- 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. Doses of adrenaline greater than 5 mcg/kg, when administered submucosally, may produce multiple ventricular arrhythmias.
- 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.
- In the majority of cases where a drug treatment is indispensable, there is no reason to suspend it before general anaesthesia. It suffices to inform the anaesthetist about it.
- All commonly used muscle relaxants are markedly potentiated by isoflurane, the effect being most profound with non-depolarizing agents. Neostigmine has an effect on the nondepolarising relaxants, but has no effect on the relaxing action of isoflurane itself. Thus it is recommended that approximately one third to one half of the usual dose of these substances be administered. The disappearance of the myoneural effect takes longer with isoflurane than with other conventional anaesthetics.

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

MAC (minimum alveolar concentration) is reduced by concomitant administration of N2O in adults (see section 4.2).

4.6 Fertility, pregnancy and lactation

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.

Use in Caesarean Section

Isoflurane, in concentrations up to 0.75%, has been shown to be safe for the maintenance of anaesthesia for caesarean section (please refer to section 4.4).

Isoflurane relaxes the uterus muscle, and the lowest possible concentration of isoflurane should be used in obstetrical operations.

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.

4.7 Effects on ability to drive and use machines

The medicinal product can have influence on driving and using machines. The patient should not drive or use machines for at least 24 hours after 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 and liver adverse reactions (please refer to section 4.4 and 4.8). Shivering, nausea, vomiting and ileus have been observed in the postoperative period.

Cardiac arrest has been observed with general inhalation anesthetic drugs including isoflurane.

b. Tabulated summary of adverse reactions

The following table displays adverse reactions reported in clinical trials and from post-marketing experience. Where frequency cannot be estimated from the available data, it is shown as “not known”.

Summary of Most Frequent Adverse Drug Reactions		
SOC	Frequency	Adverse Reactions
Blood and lymphatic system disorders	Very Rare	Carboxyhaemoglobinaemia ²
	Common	Leucocytosis ¹
Immune system disorders	Not known	Anaphylactic reaction ¹

	Not known	Hypersensitivity ¹
Metabolsim and nutrition disorders	Not known	Hyperkalaemia ²
	Common	Blood glucose increased
	Common	Increased Bromsulphthalein retention
Psychiatric disorders	Not known	Delirium
	Not known	Agitation
	Not known	Mood altered ⁵
Nervous system disorders	Not known	Convulsion
	Not known	Mental impairment ⁴
Cardiac disorders	Common	Arrhythmia
	Not known	Bradycardia
	Not known	Cardiac arrest
	Not known	Electrocardiogram QT prolonged
	Not known	Tachycardia
Vascular disorders	Common	Torsade de pointes
	Not known	Hypotension ²
		Haemorrhage ³
Respiratory, thoracic and mediastinal disorders	Rare	Bronchospasm ²
	Not known	Dyspnoea ¹
	Not known	Wheezing ¹
	Common	Respiratory depression ²
	Rare	Laryngospasm ²
	Common	Cough
Gastrointestinal disorders	Rare	Postoperative Ileus
	Uncommon	Vomiting
	Uncommon	Nausea
Hepatobiliary disorders	Very Rare	Hepatic necrosis ²
	Not known	Hepatocellular injury ²
	Not known	Blood bilirubin increased.
	Rare	Impaired Liver Function
	Rare	Icterus
	Rare	Hepatitis
Skin and subcutaneous tissue disorders	Not known	Swelling face ¹
	Not known	Dermatitis contact ¹
	Not known	Rash ¹
Renal and urinary disorders	Common	Blood creatinine increased
	Not known	Blood urea decreased
General disorders and administration site conditions	Common	Chills
	Rare	Hyperthermia malignant ²
	Not known	Chest discomfort ¹
Investigations	Not known	Hepatic enzyme increased ²
	Not known	Fluoride increased ¹
	Not known	Electroencephalogram abnormal
	Common	Blood cholesterol decreased
	Common	Blood alkaline phosphatase decreased
	Not known	

		Blood creatine phosphokinase increased
Musculoskeletal and connective tissue disorders	Not known Not known	Myoglobinuria Rhabdomyolysis

¹See 4.8(c)

²See 4.4

³In patients undergoing gynaecological surgical procedures involving uterine curettage. 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.

ADR frequency is based upon the following scale: Very Common (≥1/10); Common (≥1/100 - <1/10), Uncommon (≥1/1,000 - <1/100), Rare (≥1/10,000 - <1/1,000), Very Rare (<1/10,000)

c. Description of selected adverse reactions

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.

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 4.4.)

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

Elderly:

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

4.9 Overdose

In case of overdosage, stop administration of the anaesthetic agent, check whether air passages are open, and depending on the circumstances, continue with assisted or controlled respiration using pure oxygen.

Hypotension and respiratory depression have been observed.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Isoflurane is an inhalation-type anaesthetic, belonging to the group of halogenated anaesthetics. Induction and recovery from anaesthesia take place rapidly with isoflurane.

Isoflurane has the slightly irritating odour of ether, which can limit the speed of induction.

Pharyngeal and laryngeal reflexes are rapidly diminished as a result of which tracheal intubation is rendered easy.

5.2 Pharmacokinetic properties

AErrane is metabolised minimally in comparison to other halogenated anaesthetics. On average 95% of the AErrane is recovered in the expired air; 0.2% of the AErrane that is taken up within the body is metabolised. The principal metabolite is trifluoroacetic acid. The average serum level of inorganic fluoride in patients administered AErrane anaesthesia is between 3 and 4 micromol/litre.

In patients anaesthetised with isoflurane, the mean serum concentration of inorganic fluorides is usually less than 5 micromol/litre and occurs about four hours after anaesthesia, returning to normal levels within 24 hours. This should not alter renal function in a normal subject.

Although peak inorganic fluoride concentrations which result from the breakdown of isoflurane are generally much lower than those considered to be 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.

5.3 Preclinical safety data

No special data.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

AErrane is supplied in 100 ml and 250 ml round amber-coloured, Type III glass bottles with phenolic or polypropylene resin screw caps. The closure contains a LDPE liner.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

See under section 4.2, Posology and Method of Administration.

Any discarded anaesthetic should be collected in a glass or plastic container, which can be sealed and disposed of through the hospital’s waste disposal service.

7 MARKETING AUTHORISATION HOLDER

Baxter Healthcare Ltd.
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 Thetford
 Norfolk
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8 MARKETING AUTHORISATION NUMBER

PA 0167/106/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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