

# Data Sheet

## AERRANE

*Isoflurane USP*

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### Presentation

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Chemical Name : 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether. M.W.184.5.

CAS Number: 26675-45-7

Some physical constants are:

Molecular weight 184.5

Boiling point at 760 mmHg 48.5°C (ncorr.)

Refractive index 1.2990 - 1.3002

Specific gravity 25°/25°C 1.496

Vapour pressure in mmHg

20°C 238

25°C 295

30°C 367

35°C 450

Isoflurane is a clear, colourless, stable volatile liquid containing no additives or chemical stabilisers; it has a mildly pungent, musty, ethereal odour.

Isoflurane does not decompose in the presence of soda lime, and does not attack aluminium, tin, brass, iron or copper.

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### Pharmacology

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**Pharmacodynamic properties**

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

AERRANE 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.

### **Pharmacokinetic properties**

AERRANE is metabolised minimally in comparison to other halogenated anaesthetics such as enflurane or halothane. On average 95% of the AERRANE is recovered in the expired air; 0.2% of the AERRANE that is taken up with 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  $\mu\text{mol/litre}$ .

In patients anaesthetised with AERRANE, the mean peak serum concentration of inorganic fluorides is usually less than 5  $\mu\text{mol/litre}$  and occurs about four hours after anaesthesia, returning to normal levels within 24 hours. This should not alter renal function in a normal subject.

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## **Indications**

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AERRANE is a volatile halogenated anaesthetic for general inhalation anaesthesia.

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## **Contraindications**

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AERRANE is contraindicated in those patients with:

- Hypersensitivity to halogenated anaesthetics
- Known or suspected genetic disposition toward malignant hyperthermia
- Patients with a history of malignant hyperthermia, or in whom liver dysfunction, jaundice or unexplained fever, leucocytosis, or eosinophilia has occurred after a previous halogenated anaesthetic administration.
- Obstetric operation.
- Nonselective MAOI (see INTERACTIONS).

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## **Precautions**

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AERRANE must only be used by a licenced anaesthetist. Since the depth of anaesthesia can change easily and rapidly with AERRANE, only vaporisers that have been specially calibrated for this product may be used. 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.

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. Cirrhosis, viral hepatitis, or other pre-existing liver disease can be a reason to select an anaesthetic other than a halogenated anaesthetic.

AERRANE is a profound respiratory depressing agent 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.

Relatively little metabolism of AERRANE occurs in the human body. In the post operation period only 0.17% of the AERRANE taken up can be recovered as urinary metabolites. Peak serum inorganic fluoride values usually average less than 5 mmol/litre and occur about four hours after anaesthesia, returning to normal levels within 24 hours. No signs of renal injury have been reported after AERRANE administration.

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.

Patients with Myasthenia Gravis are extremely sensitive to medicines that produce respiratory depression. These effects are potentiated with some general anaesthetics. AERRANE 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; but tends to rise in the course of deeper anaesthesia. An increase in intracranial pressure may be averted or abolished by hyperventilation of the subject before or during anaesthesia. AERRANE should not be administered to patients who can develop broncho-constriction since bronchospasm can occur. In the case of neurosurgical operations, respiration should be adequately checked. As with other halogenated anaesthetics, AERRANE increases the flow of blood through the brain and is accompanied by a transient increase in cerebrospinal fluid pressure. In most cases, this pressure increase can be prevented by hyperventilation.

AERRANE can produce a coronary vasodilation at the arteriolar level in selected animal models; the drug is probably also a coronary dilator in humans. AERRANE, 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 AERRANE is associated with coronary steal or myocardial ischaemia in patients with coronary artery disease. However, due to the phenomenon of "coronary steal" isoflurane should be used with caution in patients with coronary artery disease. In particular, patients with subendocardial ischaemia may be considered to be more susceptible.

In light of the fact that AERRANE 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 in children, saliva flow and tracheobronchial secretion can increase and can be the cause of laryngospasm.

In the case of patients who have undergone an abortion, an increased loss of blood has been found. A transient increase in bromosulfthalein retention, blood glucose and serum creatinine with a decrease in the serum urea level, serum cholesterol level and alkaline phosphatase level has been observed.

AERRANE, as with other halogenated anaesthetics, has been reported to interact with dry carbon dioxide absorbents to form carbon monoxide. In order to minimise the risk of formation of carbon monoxide in rebreathing circuits and the possibility of elevated carboxyhaemoglobin levels, fresh (moist) carbon dioxide absorbents should be used.

In addition, consideration should be given to direct measurement of carboxyhaemoglobin levels in patients on closed circuit anaesthesia with isoflurane, if oxygen desaturation develops which does not respond to usual corrective steps.

### **Malignant Hyperthermia**

In the case of sensitive individuals, AERRANE anaesthesia can induce a hypermetabolic state in the skeletal muscles, which leads to a high oxygen consumption and a clinical syndrome that is known as malignant hyperthermia. The clinical syndrome is signalled by hypercapnia, and may include muscle rigidity, tachycardia, tachypnoea, cyanosis, arrhythmias, and/or unstable blood pressure. An increase in overall metabolism may be reflected in an elevated temperature. Some of these nonspecific signs may also appear during light anaesthesia: acute hypoxia, hypercapnia, and hypovolaemia. Treatment of malignant hyperthermia includes discontinuation of triggering agents, administration of intravenous 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 monitored and sustained if possible.

### **Perioperative Hyperkalaemia**

Use of inhaled anaesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias, some fatal, in patients during the postoperative period. Patients with both latent and 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.

### ***Pregnancy (Category B3) & Lactation***

All general anaesthetics cross the placenta and carry the potential to produce central nervous system and respiratory depression in the newborn infant. In routine practice this does not appear to be a problem: however, in the compromised foetus, careful consideration should be given to this potential depression, and to the selection of anaesthetic drugs, doses and techniques.

Concerning the use of this substance in pregnancy in the case of humans, adequate data do not exist in order to judge possible injuriousness. In regard to effects in animal tests, adequate data do not exist in order to judge possible injuriousness. In light of the fact that it has not been established that AERRANE can be used safely in pregnant women, the use of this product must be avoided during pregnancy.

Insufficient information is available to recommend use in pregnancy or obstetrics. Breast feeding should not be given for up to 12 hours after the termination of anaesthesia.

Increased blood loss has been observed in patients undergoing uterine curettage.

### **Effects on Ability to Drive and Use Machines**

Following anaesthesia with AERRANE, the patient must not drive or operate a machine for 24 hours. The patient should only be sent home with an escort, and should not consume any alcohol.

### ***Interaction with Other Medicaments and Other Forms of Interaction***

The simultaneous administration of AERRANE and the following products requires strict supervision of the clinical and biologic condition of the patient.

### **Contraindicated combination:**

Nonselective MAOI: Risk of crisis during the operation. Treatment should be stopped 15 days prior to surgery.

### **Combinations advised against:**

Beta-sympathomimetics (isoprenaline) and alpha- and beta-sympathomimetics (adrenaline; noradrenaline): risk of serious ventricular arrhythmia as a result of an increase in heart rate.

### **Combinations requiring precautions in using:**

Beta-blockers: Risk of blockage of the cardiovascular compensation mechanism, as a result of which negative inotropic effects are intensified. The action of beta-blockers can be suppressed during the operation with the use of beta-sympathomimetic agents. In general, any medication with a beta-blocker need not be stopped and an abrupt reduction of the dosage should be avoided.

Isoniazid: Risk of potentiating the hepatotoxic effect, with increased formation of toxic metabolites of isoniazid. Treatment with isoniazid should be suspended one week before the operation and should not be resumed until 15 days afterward.

Adrenaline utilised for its local haemostatic action, 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 AERRANE than in the case of other halogenated anaesthetics. Thus, the dosage should be limited to, for example, 0.1 mg adrenaline within 10 minutes or 0.3 mg within one hour in adults.

Indirect sympathomimetics (amphetamines and their derivatives; psychostimulants, appetite suppressants, ephedrine and its derivatives): Risk of intraoperative hypersensitivity episodes. In the case of a planned operation, it is preferable to interrupt the treatment a few days before the operation.

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.

Muscle relaxing agents: Risk of intensification of the action of depolarising relaxants and, in particular, nondepolarising relaxants. 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 AERRANE than with other conventional anaesthetics. Neostigmine has an effect on the nondepolarising relaxants, but has no effect on the relaxing action of AERRANE itself.

Morphine analgesics: These products potentiate the depressive action of AERRANE on respiration.

Calcium antagonists: AERRANE may lead to marked hypotension in patients treated with calcium antagonists, particularly dihydropyridine derivatives.

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## Adverse Reactions

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- Arterial hypotension: This is dependent on the dose.
- Increase in heart rate: This is intensified in case of the existence of hypercapnia. Serious ventricular rhythm disorders can arise.
- Respiratory depression: Bronchospasms are observed in rare cases.
- Disturbance of the liver function, icterus, and liver damage have been observed.
- Shivering, nausea, and vomiting upon waking from anaesthesia.
- Malignant hyperthermia (see Precautions)
- The pungency of AERRANE can give rise to an irritating action on the mucous membranes during the induction of anaesthesia, which can be accompanied by coughing, respiratory depression, and a tendency toward laryngospasm (rare).
- The number of white blood cells can increase - even in the absence of surgical stress.
- Rash.

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## Dosage and Administration

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

Minimum alveolar concentration (MAC) of AERRANE in humans:

Age (years)	O <sub>2</sub> - 100%	O <sub>2</sub> + N <sub>2</sub> O (60%)
Neonates	1.60	--
1 - 6 months	1.87	--
7 - 11 months	1.80	--
1 - 2 years	1.60	--
3 - 5 years	1.62	--
6 - 10 years	1.40	0.58
10 - 15 years	1.16	0.53
Age (years)	O <sub>2</sub> - 100%	O <sub>2</sub> + N <sub>2</sub> O (70%)
26 ± 4	1.28	0.56
44 ± 7	1.15	0.50
64 ± 5	1.05	0.37

### Induction of anaesthesia

If AERRANE is used for induction of anaesthesia, a starting concentration of 0.5% is recommended. Concentrations of 1.3 - 3.0% usually bring about surgical anaesthesia within 7 to 10 minutes.

It is recommended that use be made of a hypnotic dose of a short acting barbiturate or another product such as propofol, etomidate, or midazolam in order to avoid coughing or laryngospasm, which can arise if induction is carried out with AERRANE alone or in combination with oxygen or with an oxygen-nitrous oxide mixture.

### **Maintenance of anaesthesia**

Anaesthesia can be maintained during surgery using a concentration of 1.0 - 2.5%, with the simultaneous administration of N<sub>2</sub>O and O<sub>2</sub>.

A higher concentration of 1.5 - 3.5% of AERRANE is necessary if AERRANE is administered with pure oxygen.

### **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% O<sub>2</sub> and 50% N<sub>2</sub>O, the volume of the minimum alveolar concentration of AERRANE is approximately 0.65%.

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## **Overdosage**

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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. Support and maintain adequate haemodynamics.

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## **Presentation**

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AERRANE is supplied in 100 mL and 250 mL amber coloured glass bottles.

### **Storage**

Store bottle in an upright position. To avoid leakage, apply bottle cap firmly but not too tightly. AERRANE must be kept in the original container until immediately prior to use. Store below 30°C.

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## **Medicine Classification**

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Prescription Medicine.

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## **Name and Address**

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Baxter Healthcare Limited  
33 Vestey Drive  
Mt Wellington  
Auckland

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## **Date of Preparation**

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30 October 2006