AERRANE (Isoflurane, USP), Liquid for Inhalation

DESCRIPTION

Isoflurane 100 ml/100 ml bottle.
Chemical Name:-1-chloro-2,2,2-trifluoroethyl difluoromethyl ether.

Structural Formula:-

\[
\begin{align*}
&\text{F} \\
&\text{F} \\
&\text{C} \quad \text{C} \quad \text{O} \quad \text{C} \\
&\text{F} \quad \text{Cl} \quad \text{F}
\end{align*}
\]

CAS Number: - 26675-46-7.

Some physical constants are:-
Molecular weight 184.5
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.

**PHARMACOLOGY**

*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 µmol/L.

In patients anaesthetised with AERRANE, the mean peak serum concentration of inorganic fluorides is usually less than 5 µmol/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.

**INDICATIONS**

AERRANE is a volatile halogenated anaesthetic for general inhalation anaesthesia.

**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.

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, leukocytosis, or eosinophilia has occurred after a previous halogenated anaesthetic administration
SPECIAL WARNINGS AND PRECAUTIONS FOR USE

As with any potent general anesthetic, isoflurane should only be administered in an adequately equipped anesthetizing environment by those who are familiar with the pharmacology of the drug and qualified by training and experience to manage the anesthetized 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 anesthesia is deepened.

Since levels of anesthesia may be altered quickly and easily with isoflurane, only vaporizers 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 anesthetic 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.

Reports demonstrate that isoflurane can produce hepatic injury ranging from mild transient increases of liver enzymes to fatal hepatic necrosis in very rare instances.

It has been reported that previous exposure to halogenated hydrocarbon anesthetics, especially if the interval is less than 3 months, may increase the potential for hepatic injury. Cirrhosis, viral hepatitis, or other pre-existing liver disease can be a reason to select an anaesthetic other than a halogenated anaesthetic.

AERRANE must only be used by a licensed 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.
monitored, and assisted or controlled ventilation employed when necessary (see section Undesirable effects).

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 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 AERRANE administration.

There is insufficient experience of use in repeated anaesthesia to make a definitive 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. Isoflurane markedly increases cerebral blood flow at deeper levels of anesthesia. There may be a transient rise in cerebral spinal fluid pressure which is fully reversible with hyperventilation.

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

AERRANE should be administered with caution to patients who can develop bronchoconstriction since bronchospasms can occur (see section Undesirable effects).

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.

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

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 laryngospasms.

Increased blood losses comparable with those found following anaesthesia with other inhalation agents have been recorded with isoﬂurane in patients undergoing induced abortion.

Isoflurane relaxes the uterus muscle, and the lowest possible concentration of isoﬂurane should be used in obstetrical operations (see section Pregnancy and lactation).

Patients with Myasthenia Gravis are extremely sensitive to drugs 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
anesthesia. An increase in intracranial pressure may be averted or abolished by hyperventilation of the subject before or during anesthesia.

AERRANE should not be administered to patients who can develop bronchoconstriction since bronchospasms 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.

In the case of patients who have undergone an abortion, an increased loss of blood has been found. 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.

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.

Case reports suggest that carbon dioxide absorbents may become desiccated when fresh gases are passed through the CO₂ absorber canister at high flow rates over many hours or days. When a clinician suspects that CO₂ absorbent may be desiccated, it should be replaced before administration of 'AERRANE'.

Malignant hyperthermia
In the case of sensitive individuals, AERRANE anaesthesia may trigger a skeletal muscle hypermetabolic state in the skeletal muscles, which leads to a high oxygen demand consumption and a clinical syndrome that is known as malignant hyperthermia. The clinical syndrome includes nonspecific features such as is signalled by hypercapnia, and may include muscle rigidity, tachycardia, tachypnoea, cyanosis, arrhythmias, and/or unstable blood pressure (it also should be noted that many of these nonspecific signs may appear with light anesthesia, 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. 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 (e.g. isoflurane), 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.
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.

Rare cases of extreme heat, smoke and/or spontaneous fire in the anesthesia machine have been reported during administration of general anesthesia 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 color indicator.

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.

Ioflurane may cause a slight decrease in intellectual function for 2-4 days following anesthesia. 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 section Effects on ability to drive and use machines).

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

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

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.

**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

(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.
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 or 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.

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:**

**Combinations advised against:**

Beta-sympathomimetics (isoprenaline) and alpha- and beta-sympathomimetics (epinephrine or adrenaline; norepinephrine or noradrenaline) should be administered with caution during isoflurane narcosis, due to a potential risk of serious ventricular arrhythmia as a result of an increase in heart rate.

Nonselective MAOI: Risk of crisis and hemodynamic instability during the 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. 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.

**Epinephrine** (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 halothane other halogenated anaesthetics. Thus, the dosage should be limited to, for example, 0.1 mg epinephrine (adrenaline) within 10 minutes or 0.3 mg within one hour in adults. Doses of adrenaline greater than 5 mcg/kg, when administered submucosally, may produce multiple ventricular arrhythmias.

Indirect 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. Intraoperative hypersensitivity episode. 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:** All commonly used muscle relaxants are markedly potentiated by isoflurane, the effect being most profound with nondepolarizing 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.

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

**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. 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 N20 in adults (see Dosage and Administration).

**PREGNANCY AND LACTATION**

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

**Use in Caesarean Section**
Isoflurane, in concentrations up to 0.75%, has been shown to be safe for the maintenance of anesthesia for cesarean section (see section Special warnings and special precautions for use).

**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.

**Pregnancy & Lactation**
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

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.

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.

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 Special warnings and precautions for use and Undesirable effects). 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. Frequency cannot be estimated from the available data, therefore it is “not known”.

<table>
<thead>
<tr>
<th>SOC</th>
<th>Frequency</th>
<th>Adverse Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Not known</td>
<td>Carboxyhaemoglobinaemia²</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Not known</td>
<td>Anaphylactic reaction ¹</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Not known</td>
<td>Hyperkalemia ²</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Not known</td>
<td>Agitation</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Not known</td>
<td>Convulsion</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Not known</td>
<td>Arrhythmia</td>
</tr>
</tbody>
</table>

Summary of Most Frequent Adverse Drug Reactions
<table>
<thead>
<tr>
<th>SOC</th>
<th>Frequency</th>
<th>Adverse Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Not known</td>
<td>Bronchospasm ¹</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Dyspnoea ¹</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Wheezing ¹</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Respiratory depression ³</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Laryngospasm ³</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Not known</td>
<td>Ileus</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Vomiting</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Nausea</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Not known</td>
<td>Hepatic necrosis ¹</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Hepatocellular injury ²</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Blood bilirubin increased</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue</td>
<td>Not known</td>
<td>Swelling face ¹</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Dermatitis contact ³</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Rash ³</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Not known</td>
<td>Blood creatinine increased</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Blood urea decreased</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Not known</td>
<td>Hyperthermia malignant ³</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Chest discomfort ³</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Chills ³</td>
</tr>
<tr>
<td>Investigations</td>
<td>Not known</td>
<td>White blood cell count increased ¹</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Hepatic enzyme increased ³</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Fluoride increased ³</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Electroencephalogram abnormal</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Blood cholesterol decreased</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Blood alkaline phosphatase decreased</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Blood creatine phosphokinase increased</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Not known</td>
<td>Myoglobinuria</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Rhabdomyolysis</td>
</tr>
</tbody>
</table>

¹ See Undesirable effects  
² Special Warnings and Precautions for use  
³ In patients undergoing induced abortion see Special Warnings and Precautions for use  
⁴ May cause a slight decrease in intellectual function for 2-4 days after anesthesia See Special Warnings and Precautions for use
Small changes in moods and symptoms may persist for up to 6 days. See Special Warnings and Precautions for use.

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 anesthetic agents, including isoflurane. These reactions have been confirmed by clinical testing (e.g., methacholine challenge). The etiology of anaphylactic reactions experienced during inhalational anesthetic 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 anesthesia, 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 anesthetic 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. (See Special warnings and precautions for use)

During the induction of anesthesia, saliva flow and tracheobronchial secretion can increase and can be the cause of laryngospasm. (See Special warnings and precautions for use)

e. Other special populations

Neuromuscular disease:
Use of inhaled anesthetic 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. (See Special warnings and precautions for use)

Elderly:
Lesser concentrations of isoflurane are normally required to maintain surgical anesthesia in elderly patients. (See Special warnings and precautions for use)

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.
Post-Marketing Events:
The following adverse events have been identified during post-approval use of isoflurane USP in United States:
Due to the spontaneous nature of these reports, the actual incidence and relationship of isoflurane, USP to these events cannot be established with certainty.

Cardiac Disorders: Cardiac arrest.

Hepatobiliary Disorders: Hepatic necrosis, Hepatic failure

Reporting of suspected adverse reactions
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form (http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il) or by email (adr@MOH.HEALTH.GOV.IL).

DOSAGE AND ADMINISTRATION
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:

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>O₂ – 100%</th>
<th>O₂ + N₂O (60%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates</td>
<td>1.60</td>
<td>-</td>
</tr>
<tr>
<td>1-6 months</td>
<td>1.87</td>
<td>-</td>
</tr>
<tr>
<td>7-11 months</td>
<td>1.80</td>
<td>-</td>
</tr>
<tr>
<td>1-2 years</td>
<td>1.60</td>
<td>-</td>
</tr>
<tr>
<td>3-5 years</td>
<td>1.62</td>
<td>-</td>
</tr>
<tr>
<td>6-10 years</td>
<td>1.40</td>
<td>0.58</td>
</tr>
<tr>
<td>10-15 years</td>
<td>1.16</td>
<td>0.53</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>O₂ – 100%</th>
<th>O₂ + N₂O (70%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>26 ± 4</td>
<td>1.28</td>
<td>0.56</td>
</tr>
<tr>
<td>44 ± 7</td>
<td>1.15</td>
<td>0.50</td>
</tr>
<tr>
<td>64 ± 5</td>
<td>1.05</td>
<td>0.37</td>
</tr>
</tbody>
</table>

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 N₂O and O₂.

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% O₂ and 50% N₂O, the volume of the minimum alveolar concentration of AERRANE is approximately 0.65%.

**PRECLINICAL SAFETY DATA**

No special data.

**OVERDOSAGE**

In case of overdosage, stop administration of the anaesthetic agent.

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. Check whether air passages are open, and depending on the circumstances, continue with assisted or controlled respiration using pure oxygen.

**PRESENTATION**

AERRANE is supplied in 6x 100 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.**

**REGISTRATION NUMBER:** 051 79 23531 00.

**MANUFACTURER**

Baxter Healthcare Corporation

U.S.A.
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