

## ISOFLURANE

### CORE SAFETY PROFILE

#### 4.3 Contraindications

Isoflurane is contraindicated in patients with known sensitivity to isoflurane or other halogenated anesthetics. It is also contraindicated in patients with known or suspected genetic susceptibility to malignant hyperthermia.

#### 4.4 Special warnings and precautions for use

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.

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 induced abortion.

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

Isolated cases of increased carboxyhemoglobin have been reported with the use of halogenated inhalation agents with a -CF<sub>2</sub>H 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 CO<sub>2</sub> 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 CO<sub>2</sub> absorbents, specifically those containing potassium hydroxide (e.g. Baralyme). When a clinician suspects that the CO<sub>2</sub> absorbent may be desiccated, it should be replaced before administration of isoflurane. The color indicator of most CO<sub>2</sub> 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. CO<sub>2</sub> absorbents should be replaced routinely regardless of the state of the color indicator.

#### *General*

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.

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 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 preexisting liver disease can be a reason to select an anesthetic other than a halogenated anesthetic.

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

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.

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-depolarizing agents.

Isoflurane 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 (please refer to section 4.7).

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 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).

During the induction of anesthesia, 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 isoflurane is used in small children due to limited experience with this patient-group.

### ***Malignant Hyperthermia***

In susceptible individuals, isoflurane anesthesia 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 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 CO<sub>2</sub> absorption system (hot canister). PaO<sub>2</sub> and pH may decrease,

and hyperkalemia and a base deficit may appear. 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.

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. 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.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

##### *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 during the operation. Treatment should be stopped 15 days prior to surgery.

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

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

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

Cardiovascular compensation reactions may be impaired by beta-blockers.

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

Calcium antagonists, in particular dihydropyridine 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-depolarizing agents. Neostigmine has an effect on the nondepolarising relaxants, but has no effect on the relaxing action of isoflurane itself.

MAC (minimum alveolar concentration) is reduced by concomitant administration of N<sub>2</sub>O 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.

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

##### ***Use in Cesarean Section***

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

##### ***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. Frequency cannot be estimated from the available data, therefore it is “not known”.

<b>Summary of Most Frequent Adverse Drug Reactions</b>		
<b>SOC</b>	<b>Frequency</b>	<b>Adverse Reactions</b>
Blood and lymphatic system disorders	Not known	Carboxyhaemoglobinaemia <sup>2</sup>
Immune system disorders	Not known	Anaphylactic reaction <sup>1</sup>

	Not known	Hypersensitivity <sup>1</sup>
Metabolism and nutrition disorders	Not known	Hyperkalaemia <sup>2</sup>
	Not known	Blood glucose increased
Psychiatric disorders	Not known	Agitation
	Not known	Delirium
	Not known	Mood altered <sup>5</sup>
Nervous system disorders	Not known	Convulsion
	Not known	Mental impairment <sup>4</sup>
Cardiac disorders	Not known	Arrhythmia
	Not known	Bradycardia
	Not known	Cardiac arrest
	Not known	Electrocardiogram QT prolonged
	Not known	Tachycardia
	Not known	Torsade de pointes
Vascular disorders	Not known	Hypotension <sup>2</sup>
	Not known	Haemorrhage <sup>3</sup>
Respiratory, thoracic and mediastinal disorders	Not known	Bronchospasm <sup>2</sup>
	Not known	Dyspnoea <sup>1</sup>
	Not known	Wheezing <sup>1</sup>
	Not known	Respiratory depression <sup>2</sup>
	Not known	Laryngospasm <sup>2</sup>
Gastrointestinal disorders	Not known	Ileus
	Not known	Vomiting
	Not known	Nausea
Hepatobiliary disorders	Not known	Hepatic necrosis <sup>2</sup>
	Not known	Hepatocellular injury <sup>2</sup>
	Not known	Blood bilirubin increased.
Skin and subcutaneous tissue disorders	Not known	Swelling face <sup>1</sup>
	Not known	Dermatitis contact <sup>1</sup>
	Not known	Rash <sup>1</sup>
Renal and urinary disorders	Not known	Blood creatinine increased
	Not known	Blood urea decreased
General disorders and administration site conditions	Not known	Hyperthermia malignant <sup>2</sup>
	Not known	Chest discomfort <sup>1</sup>
	Not known	Chills
Investigations	Not known	White blood cell count increased <sup>1</sup>
	Not known	Hepatic enzyme increased <sup>2</sup>
	Not known	Fluoride increased <sup>1</sup>
	Not known	Electroencephalogram abnormal
	Not known	Blood cholesterol decreased
	Not known	Blood alkaline phosphatase decreased
	Not known	Blood creatine phosphokinase increased
Musculoskeletal and connective tissue disorders	Not known Not known	Myoglobinuria rhabdomyolysis

<sup>1</sup>See 4.8(c)

<sup>2</sup>See 4.4

<sup>3</sup>In patients undergoing induced abortion. See 4.4.

<sup>4</sup>May cause a slight decrease in intellectual function for 2-4 days after anesthesia. See 4.4.

<sup>5</sup>Small changes in moods and symptoms may persist for up to 6 days. See 4.4.

### *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  $\mu\text{mol/l}$  in one study) could cause renal toxicity, as these are well below the proposed threshold levels for kidney toxicity.

### *d. Pediatric 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 4.4.)

During the induction of anesthesia, 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 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 4.4.)

#### **Elderly:**

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

## **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 anesthesia.