PRODUCT MONOGRAPH

[Pr] Isoflurane USP

(Isoflurane, 99.9%)

Inhalation Anesthetic

Fresenius Kabi Canada Ltd.
165 Galaxy Blvd, Suite 100
Toronto, ON M9W 0C8

Date of Revision:
May 23, 2018

Control No.: 215732

Table of Contents

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(Isoflurane, 99.9%)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Inhalation	Liquid / 99.9%	None

INDICATIONS AND CLINICAL USE

Isoflurane is indicated for:

- induction and maintenance of general anesthesia.

Geriatrics (> 65 years of age):
The minimum alveolar concentration (MAC) of isoflurane decreases with increasing patient age. The dose should be adjusted accordingly. See table in DOSAGE AND ADMINISTRATION.

Pediatrics (0 – 16 years of age):
MAC values for children up to 5 years of age, including those for preterm neonates, are available. Isoflurane MAC decreases with increasing age, except for both term and preterm neonates, measured approximately at 1 month of age. See table in DOSAGE AND ADMINISTRATION.

CONTRAINDICATIONS

Isoflurane is contraindicated in patients:

- with known hypersensitivity to isoflurane or to other halogenated inhalational anesthetics.
- with a history of hepatitis due to a halogenated inhalational anesthetic or in whom liver dysfunction, jaundice or unexplained fever, leucocytosis, or eosinophilia has occurred after a previous halogenated anesthetic administration (see WARNINGS AND PRECAUTIONS).
- with known or suspected genetic susceptibility to malignant hyperthermia, or with a history of malignant hyperthermia (see WARNINGS AND PRECAUTIONS).
- in whom general anesthesia is contraindicated.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Isoflurane should be administered only by persons trained in the administration of general anesthesia.**
- **Facilities for maintenance of a patent airway, artificial ventilation, oxygen enrichment, and circulatory resuscitation must be immediately available.**
- **Isoflurane may trigger Malignant Hyperthermia in susceptible individuals and fatal outcomes have been reported (see Malignant Hyperthermia section below).**
- **Isoflurane use may lead to Perioperative Hyperkalemia in patients with neuromuscular disorders (see Hyperkalemia section below).**

General

Deliver isoflurane from a vaporizer specifically designed and designated for use with isoflurane. Monitoring of end-tidal concentration may be considered.

The safety of repeated anesthesia with isoflurane has not been studied. As with all halogenated anesthetics, repeated anesthesia within a short period of time should be approached with caution.

Patients should be advised that performance of activities requiring mental alertness and motor coordination, such as driving a vehicle or operating machinery, may be impaired for at least 24 hours following administration of general anesthesia.

The following reactions have been reported following occupational exposure to isoflurane: dyspnea, bronchospasm, stridor, cough, dizziness, paresthesia, hepatic reactions, flushing, rash, contact dermatitis, erythema, periorbital edema, eye irritation, conjunctival hyperemia, and headache. See ADVERSE REACTIONS, Post-Market Adverse Drug Reactions.

Cardiovascular

Use in Patients With or at Risk for Elevations of Intracranial Pressure
Isoflurane can increase cerebral blood flow and hence intracranial pressure (ICP), and therefore should be used with special care in patients with pre-existing increases in intracranial pressure. In patients with or at risk for elevations of ICP, isoflurane should be administered cautiously and in conjunction with ICP-reducing measures (e.g., optimized hyperventilation).

Use in Hypovolemic, Hypotensive, or Hemodynamically Compromised Patients
Isoflurane causes a dose-dependent reduction in systemic vascular resistance and blood pressure. Particular care must be taken when selecting the dosage for patients who are hypovolemic, hypotensive, or otherwise hemodynamically compromised, for example, due to concomitant medications. Excessive decreases in blood pressure may be related to depth of anesthesia and

respond to reducing the inspired concentration of isoflurane.

Use in Patients with Coronary Artery Disease
In patients with coronary artery disease, maintenance of normal hemodynamics is important in order to avoid myocardial ischemia. Isoflurane can cause dose dependent coronary vasodilation and has been shown to divert blood from collateral-dependent myocardium to normally perfused areas in an animal model ("coronary steal"). The extent to which coronary steal occurs in patients with steal-prone coronary anatomy is unclear. Isoflurane should be used with caution in such patients.

QT Prolongation
Caution should be exercised when administering isoflurane to susceptible patients. Isoflurane can prolong the QT interval in adults and children. This effect is exacerbated by some of the patient's disease conditions or concomitant peri-operative medications (e.g., patients with congenital Long QT Syndrome or patients taking drugs that can prolong the QT interval). Isolated post-market cases of cardiac arrhythmia associated with the QT prolongation have been reported. There are very rare reports of torsade de pointes.

Endocrine and Metabolism

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 features such as high core body temperature, muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and unstable blood pressure. 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_2 absorption system (hot canister). PaO_2 and pH may decrease, and hyperkalemia and a base deficit may appear. Treatment includes discontinuance of triggering agents (e.g., isoflurane), administration of intravenous dantrolene sodium, and application of supportive therapy. Such therapy includes vigorous efforts to decrease the patient's body temperature to normal, respiratory and circulatory support as indicated, and management of electrolyte-fluid-acid-base derangements. Renal failure may appear later, and urine flow should be sustained if possible. A number of fatal outcomes from malignant hyperthermia have been reported with isoflurane. See CONTRAINDICATIONS.

Hyperkalemia
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 intraoperatively and postoperatively. 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 creatinine 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.

Hematologic

Intraoperative elevation of blood glucose and white blood count may occur. The effect of general anesthetics on blood glucose should be taken into consideration in the management of diabetic patients.

Hepatic/Biliary/Pancreatic

Isoflurane is contraindicated in patients with a history of hepatitis due to a halogenated inhalational anesthetic or in whom liver dysfunction, jaundice or unexplained fever, leucocytosis, or eosinophilia has occurred after a previous halogenated anesthetic administration.

Cases of mild, moderate, and severe postoperative hepatic dysfunction or hepatitis with or without jaundice, including fatal hepatic necrosis and hepatic failure, have been reported with isoflurane. As with other halogenated anesthetics, isoflurane may cause sensitivity hepatitis in patients who have been sensitized by previous exposure to a halogenated anesthetic. Such reactions may also occur after the first exposure to isoflurane.

Although the mechanism by which this occurs is still unclear, data from studies on halothane suggests that metabolism by cytochrome P450 2E1 (CYP2E1) catalyzes formation of trifluoroacetylated haptens, which may be implicated as target antigens in the mechanism of halothane-induced hepatitis. Although other halogenated anesthetics are believed to be metabolized to a much lesser degree by the CYP2E1 system (20% by halothane compared to 0.2% isoflurane), the reported hepatic injuries share similarities with that associated with halothane.

In patients with pre-existing hepatic abnormalities or under treatment with drugs known to cause hepatic abnormalities, clinical judgment should be exercised and appropriate alternative general anesthesia should be considered. Specialized care is recommended when a patient presents with any postoperative hepatic dysfunction after receiving a halogenated inhalational anesthetic.

Psychiatric

Isoflurane may cause a decrease in intellectual function as well as changes in mood for several days after general anesthesia.

Respiratory

Isoflurane inhibits spontaneous respiration, which is enhanced with concurrent use of other inhalational and intravenous anesthetics. Respiration must be closely monitored and supported by assisted or controlled ventilation when necessary. Excessive respiratory depression may be related to depth of anesthesia and responds to decreasing the inspired concentration of isoflurane.

Hypersensitivity Reactions

Allergic-type hypersensitivity reactions, including anaphylaxis, have been reported with isoflurane. Manifestations of such reactions have included hypotension, rash, difficulty breathing and cardiovascular collapse. Symptomatic management, as appropriate, is recommended as per standard of care.

Sexual Function/Reproduction

Isoflurane exerts a relaxant effect on uterine smooth muscle. Blood loss during intrauterine procedures is increased when halogenated agents such as isoflurane are used for anesthesia.

Special Populations

Isoflurane should only be used in pregnant women, including women in labour and delivery, or young children when its benefits outweigh potential risks. Patients should be followed up post-operatively after exposure to isoflurane as appropriate to identify potential adverse effects (see TOXICOLOGY, Reproductive and Teratology).

Pregnant Women: The safety of isoflurane anesthesia to mother and fetus has not been studied.

Women in Labour and Delivery: Safety and efficacy of isoflurane administration during labour and vaginal delivery have not been adequately studied.

Cesarean Section: The use of isoflurane as part of general anesthesia for elective cesarean section has been described in the literature. Isoflurane should be used only if the potential benefit justifies the potential risk.

Isoflurane exerts a relaxant effect on uterine smooth muscle. This can lead to increased blood loss in situations where uterine muscle contraction aids hemostasis, such as in obstetric surgery and in patients undergoing intrauterine procedures.

Nursing Women: Because there is insufficient information regarding the excretion of isoflurane in human milk, the potential risks and benefits for each specific patient should be carefully considered before isoflurane is administered to nursing women.

Pediatrics (0 - 16 years of age): Isoflurane MAC decreases with increasing age, except for both term and preterm neonates, measured approximately at 1 month of age. See table in DOSAGE AND ADMINISTRATION. During the induction of anesthesia, saliva and tracheobronchial secretion can increase and can be the cause of laryngospasm, particularly in children.

Geriatrics (> 65 years of age): With adults, isoflurane MAC decreases with increasing age. See table in DOSAGE AND ADMINISTRATION.

Monitoring and Laboratory Tests

All patients anesthetized with isoflurane should be continuously monitored (e.g., monitoring of the electrocardiogram, blood pressure, oxygen saturation, and end tidal CO_2). Respiration must be monitored closely and supported when necessary.

Bromsulfalein (BSP) retention is mildly elevated postoperatively in some cases.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse event information is derived from controlled clinical studies of adult and pediatric patients exposed to isoflurane. The studies were conducted using a variety of premedications, other anesthetics, and surgical procedures of varying length. In these controlled studies, isoflurane was used in a total of 2830 cases: 2643 adults and 187 children 19 years of age or younger. The estimated frequencies for adverse events were based on various pooled data sets. Due to the differences in the sizes of the available pooled data sets, the denominators presented in the clinical trial adverse events table vary.

The most serious reported treatment-emergent adverse events in alphabetical order are apnea, atrioventricular block, bradycardia, bronchospasm, cardiac arrest, hepatic failure, hypercapnia, hyperkalemia, hypotension, hypoxia, malignant hyperthermia, respiratory depression, and ventricular arrhythmias including fibrillation.

The most frequent treatment-emergent adverse events (incidence > 10%) are white blood cell count increased, agitation, breath holding, cough, nausea, and chills/shivering.

All of the treatment-emergent adverse events listed in the table below may result in the need for clinical investigation and treatment.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

The following treatment-emergent adverse events were identified from controlled clinical studies of adult and pediatric subjects exposed to isoflurane. The studies were conducted using a variety of premedications, other anesthetics, and surgical procedures of varying lengths.

System Organ Class (SOC)	Adverse Reaction	Frequency (%)	
BLOOD AND LYMPHATIC SYSTEM DISORDERS	**White blood cell count increased**	> 10%	
CARDIAC DISORDERS	**Ventricular arrhythmia (intraoperative)**	**Induction** 2% (45/2161)	**Maintenance** 3% (60/2253)
	Nodal arrhythmia (intraoperative)	**Induction** 4% (87/2161)	**Maintenance** 2% (38/2253)
	Atrial arrhythmia (intraoperative)	**Induction** 2% (35/2161)	**Maintenance** 2% (50/2253)
	Arrhythmia (postoperative)	1% (32/2830)	
GASTROINTESTINAL DISORDERS	**Nausea (Recovery)**	15% (436/2830)	
	Vomiting (Recovery)	10% (269/2830)	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**Chills/shivering**	14% (237/1691)	
NERVOUS SYSTEM DISORDERS	**Agitation (Excitement)**	**Induction** 52% (267/515)	Data Not Available
	Movement	Data Not Available	**Maintenance** 2% (52/2830)
PSYCHIATRIC DISORDERS	**Delirium**	6% (176/2830)	
RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS	**Breath holding**	**Induction** 24% (123/515)	**Maintenance** 1% (4/359)
	Cough	**Induction** 28% (145/515)	**Maintenance** 4% (15/359)
	Laryngospasm	**Induction** 8% (41/515)	Refer to **Less Common Clinical Trial Adverse Drug Reactions (< 1%)**

Overall frequency of "White blood cell count increased" observed during clinical studies was very common. Increases in white blood cell count were reported to rise for all patients in the first 1 to 2 days and 3 to 5 days postoperatively.

The frequencies cannot be calculated from the database for the adverse events listed below.

GASTROINTESTINAL DISORDERS: Post-operative Ileus

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS: Asthenia, fatigue

HEPATOBILIARY DISORDERS: Blood bilirubin increased, bromosulphthalein clearance

decreased, alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased

METABOLISM AND NUTRITION DISORDERS: Blood glucose increased

MUSCULOSKELETAL, CONNECTIVE TISSUE AND BONE DISORDERS: Myalgia

NERVOUS SYSTEM DISORDERS: Ataxia, dizziness, drowsiness, intellectual function decreased

PSYCHIATRIC DISORDERS: Confusional state, nervousness

VASCULAR DISORDERS: Hypotension (intraoperative), hypertension (intraoperative)

Less Common Clinical Trial Adverse Drug Reactions (<1%)

GASTROINTESTINAL DISORDERS: Vomiting (induction), retching (induction and maintenance)

NERVOUS SYSTEM DISORDERS: Convulsive pattern on electroencephalogram, seizure

PSYCHIATRIC DISORDERS: Mood changes, nightmare

RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS: Laryngospasm (maintenance), secretions (induction)

SKIN AND SUBCUTANEOUS TISSUE DISORDERS: Diaphoresis (induction)

VASCULAR DISORDERS: Hypotension (postoperative), hypertension (postoperative)

Post-Market Adverse Drug Reactions

The following adverse events have been reported in the post-marketing experience, listed by MedDRA System Organ Class (SOC), then by Preferred Term in order of severity.

Perioperative use:

BLOOD AND LYMPHATIC SYSTEM DISORDERS: Carboxyhemoglobin increased

CARDIAC DISORDERS: Cardiac arrest, ventricular fibrillation, torsade de pointes, myocardial infarction, myocardial ischemia, atrioventricular block complete, atrioventricular block second degree, atrial fibrillation, electrocardiogram QT prolonged, atrioventricular block first degree, ventricular tachycardia, ventricular extrasystoles, tachycardia, bradycardia, cardiac output decreased

GASTROINTESTINAL DISORDERS: Pancreatitis

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS: Malignant hyperthermia, hypothermia

HEPATOBILIARY DISORDERS: Hepatic failure, hepatic necrosis, hepatitis fulminant, cholestatic hepatitis, hepatitis, hepatic steatosis, jaundice, gamma-glutamyltransferase increased

IMMUNE SYSTEM DISORDERS: Anaphylactic reaction

INJURY, POISONING, AND PROCEDURAL COMPLICATIONS: Unwanted awareness during anesthesia

METABOLISM AND NUTRITION DISORDERS: Hyperkalemia

MUSCULOSKELETAL, CONNECTIVE TISSUE AND BONE DISORDERS: Rhabdomyolysis

NERVOUS SYSTEM DISORDERS: Brain edema, intracranial pressure increased, migraine, myoclonus, nystagmus, pupils unequal, headache

PSYCHIATRIC DISORDERS: Withdrawal syndrome (following multi-day exposure; symptoms include seizure, hallucination, ataxia, agitation, confusion)

RENAL AND URINARY DISORDERS: Acute renal failure, oliguria

RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS: Apnea, hypoxia, bronchospasm, airway obstruction, respiratory depression, hypercapnia, stridor, hiccups

SKIN AND SUBCUTANEOUS TISSUE DISORDERS: Rash

VASCULAR DISORDERS: Flushing

<u>Occupational Exposure</u>:

INJURY, POISONING, AND PROCEDURAL COMPLICATIONS: Dyspnea, bronchospasm, stridor, cough, dizziness, paresthesia, hepatic reactions, flushing, rash, contact dermatitis, erythema, periorbital edema, eye irritation, conjunctival hyperemia, headache

DRUG INTERACTIONS

Serious Drug Interactions

- In Patients with latent as well as overt muscular dystrophies, particularly Duchenne Muscular Dystrophy, concomitant use with succinylcholine is associated with hyperkalemia and cardiac arrhythmias (see WARNINGS AND PRECAUTIONS).

Overview

The minimum alveolar concentration (MAC) for isoflurane is reduced by concomitant inhalational anesthetics, such as N_2O, and intravenous anesthetics, such as opioids and benzodiazepines. Commonly used muscle relaxants are potentiated by isoflurane.

Drug-Drug Interactions

Opioids

The minimum alveolar concentration (MAC) for isoflurane is reduced by concomitant administration of intravenous anesthetics, such as opioids and benzodiazepines. Opioids such as fentanyl and its analogues, when combined with isoflurane, may lead to a synergistic fall in blood pressure and respiratory rate.

Nitrous Oxide

N_2O decreases the MAC of isoflurane (see DOSAGE AND ADMINISTRATION).

Neuromuscular Blocking Agents

Isoflurane decreases the required doses of neuromuscular blocking agents. Isoflurane potentiates all commonly used muscle relaxants, the effect being most profound with the nondepolarizing type. Therefore, less than the usual amounts of such agents should be used. In general, anesthetic concentrations of isoflurane at equilibrium reduce the ED95 of succinylcholine, atracurium, pancuronium, rocuronium and vecuronium by approximately 25 to 40% or more compared to N_2O/opioid anesthesia. Neostigmine reverses the effects of nondepolarizing muscle relaxants, but does not reverse the direct neuromuscular depression of isoflurane.

Epinephrine / Adrenaline

Isoflurane is similar to sevoflurane in the sensitization of the myocardium to the arrhythmogenic effect of exogenously administered adrenaline. The threshold dose at which submucosally administered adrenaline produces multiple ventricular arrhythmias has been established at 5 mcg/kg body weight.

Calcium Antagonists

Isoflurane may lead to marked hypotension in patients treated with calcium antagonists.

Concomitant Use of Beta Blockers Inhibitors

Concomitant use of beta blockers may exaggerate the cardiovascular effects of inhalational anesthetics, including hypotension and negative inotropic effects.

Concomitant Use of MAO Inhibitors

Concomitant use of Monoamine Oxidase (MAO) inhibitors and inhalational anesthetics may increase the risk of hemodynamic instability during surgery or medical procedures.

Concomitant Use of CYP2E1 Inducers

CYP2E1 is the predominant CYP isoform responsible for isoflurane metabolism *in vivo*. Therapeutic products and other agents that increase the activity of cytochrome P450 isoenzyme CYP2E1, such as isoniazid and alcohol, may increase the metabolism of isoflurane and lead to

significant increases in plasma fluoride concentrations. Moreover, CYP2E1 metabolic pathways may be involved in the rare hepatotoxic effects observed with halogenated anesthetics, therefore, a concomitant use of CYP2E1 inducers may potentiate this risk in susceptible patients. In contrast, disulfiram, a selective inhibitor of CYP2E1, prevents 80 – 90% of isoflurane metabolism.

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

St. John's Wort
Severe hypotension and delayed emergence from anesthesia with halogenated inhalational anesthetics have been reported in patients treated long-term with St John's Wort.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Preanesthetic Medication
Premedication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by isoflurane and that the heart rate tends to be increased. The use of anticholinergic drugs is a matter of choice.

Minimum Alveolar Concentration (MAC)
Isoflurane minimum alveolar concentration (MAC) decreases with increasing patient age, except for both term and preterm neonates, measured approximate at 1 month of age.

Isoflurane MAC values according to age are shown below for reference:

Age	Average MAC Value In 100% Oxygen	Average MAC Value In 30% Oxygen and 70% N_2O
Preterm neonates < 32 weeks gestational age	1.28 %	-
Preterm neonates 32-37 gestational age	1.41 %	-
0 – 1 month	1.60 %	-
1 – 6 months	1.87 %	-
6 – 12 months	1.80 %	-
1 – 5 years	1.60 %	-
6 – 18 years	-	-
19 – 30 years	1.28 %	0.56 %
32 – 55 years	1.15 %	0.50 %
55 – 83 years	1.05 %	0.37 %

Administration Equipment
Isoflurane is administered by inhalation. Isoflurane must be delivered from a vaporizer specifically designed and calibrated for use with isoflurane. The delivered concentration of isoflurane should be monitored.

Keyed Bottle Collar (for use with Key-fill Vaporizer) - Note that colour of keyed bottle collar will match the colour of the adaptor.

Directions for Use:
- To attach a keyed bottle adaptor, remove cap and seal from anesthetic bottle.
- Check that the anesthetic bottle neck is not chipped or damaged.
- Match keyed bottle adaptor to keyed bottle collar and screw together until tight.
- Now connect the bottle to the vaporizer filler receptacle.

Reaction with CO_2 Absorbents
Isoflurane, like some other inhalational anesthetics, can react with desiccated carbon dioxide (CO_2) absorbents to produce carbon monoxide which may result in elevated levels of carboxyhemoglobin in some patients. Barium hydroxide lime and sodalime become desiccated when fresh gases are passed through the CO_2 absorber canister at high flow rates over many hours. The clinician must ensure the CO_2 absorbent in use is adequately hydrated before using isoflurane.

The color indicator of most CO_2 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_2 absorbents should be replaced routinely regardless of the state of the color indicator, following current guidelines for use of anesthesiology equipment.

Induction
Induction with isoflurane in oxygen or in combination with oxygen-nitrous oxide mixtures may produce coughing, breath-holding, or laryngospasm. These difficulties may be avoided by use of a hypnotic dose of an intravenous induction agent (e.g., propofol) or a short-acting barbiturate, preceding the isoflurane mixture.

It should be considered that the risk of coughing, breath holding, laryngospasm, and bronchospasm during induction increases with the concentration of isoflurane.

Recommended Dose and Dosage Adjustment

Dosage for induction and maintenance must be individualized and titrated to the desired effect according to the patient's age, clinical status, and surgical requirements.

Induction
Inspired concentrations of 1.5 to 3.0% isoflurane with a background of 50 to 70% nitrous oxide usually produce surgical anesthesia in 7 to 10 minutes. If nitrous oxide is not used, an additional 1.0 to 1.5% isoflurane may be required for induction of anesthesia.

Maintenance
Surgical levels of anesthesia may be sustained with a 1.0 to 2.5% concentration when 50 to 70% nitrous oxide is used concomitantly. An additional 0.5 to 1.0% may be required when isoflurane is given in oxygen alone. Additional relaxation may be produced with supplemental doses of muscle relaxants.

In the absence of other complicating problems, blood pressure during maintenance varies inversely with isoflurane concentration. Hypotension may be related to depth of anesthesia and may respond to decreasing the inspired concentration of Isoflurane, if appropriate. Adequate depth of anesthesia should be maintained with isoflurane and alternative anesthetics, as appropriate, to reduce the risk of unwanted awareness during surgery.

OVERDOSAGE

Overdosage with isoflurane produces marked hypotension and may cause apnea. In the event of overdosage, or what appears to be overdosage, the following actions should be taken, as appropriate:

1. Discontinue administration of isoflurane.
2. Establish a patent airway and initiate assisted or controlled ventilation with oxygen supplementation as needed.
3. Maintain cardiovascular parameters within acceptable physiologic range.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Isoflurane is an inhalation anesthetic whose low solubility (blood/gas partition coefficient equals 1.4), permits a rapid induction of and recovery from anesthesia. The mild pungency of isoflurane may limit the rate of induction, although excessive salivation or tracheobronchial secretions do not appear to be stimulated. The level of anesthesia may be changed rapidly with isoflurane. Pharyngeal and laryngeal reflexes are readily and easily obtunded. Isoflurane is a profound respiratory depressant. An increase in anesthetic dose will decrease tidal volume without changing respiratory rate. This depression is partially reversed by surgical stimulation, even at deeper levels of anesthesia. Isoflurane evokes a sigh response reminiscent of that seen with diethyl ether and enflurane.

Typically, blood pressure decreases with induction of anesthesia but may return toward normal with surgical stimulation. Progressive increases in depth of anesthesia correspondingly decrease

blood pressure. Nitrous oxide diminishes the inspired concentration of isoflurane required to reach a desired level of anesthesia and has a favorable effect on the parameters of the anesthetic process. With controlled ventilation and normal $PaCO_2$, cardiac output is maintained despite increasing depth of anesthesia primarily through an increase in heart rate which compensates for a reduction in stroke volume. The hypercapnia which attends spontaneous ventilation during isoflurane anesthesia further increases heart rate and raises cardiac output above awake levels.

The cardiac rhythm during isoflurane anesthesia is stable. In dog studies, isoflurane has not been found to sensitize the myocardium to exogenously administered epinephrine. Limited data indicate that subcutaneous injection of 0.25 mg of epinephrine (50 mL of 1:200,000 solution) does not cause ventricular arrhythmias in patients anesthetized with isoflurane. Doubling this dose will produce ventricular extrasystoles in about half of patients anesthetized with 1.25 MAC isoflurane.

Muscle relaxation usually is adequate for intra-abdominal operations at normal levels of anesthesia. All commonly used muscle relaxants are compatible with isoflurane. Complete paralysis can be attained with small doses of muscle relaxants. Isoflurane potentiates all commonly used muscle relaxants, the effect being most profound with nondepolarizing relaxants. Neostigmine reverses the effect of nondepolarizing muscle relaxants in the presence of isoflurane but does not reverse the direct neuromuscular depression of isoflurane.

Pharmacokinetics

Metabolism: CYP2E1 is the predominant CYP isoform responsible for isoflurane metabolism *in vivo*.

The metabolism of isoflurane is low in miniature swine, black C-57 mice, and Fischer 344 rats. Less than half of one percent of the isoflurane taken up in humans can be recovered as metabolites.

In Fischer 344 rats, the peaks of inorganic fluoride ion occurred during the second 24 hours postanesthesia; all values had returned to baseline 2 to 3 days later (organic fluoride to inorganic fluoride ratio 0.53:1). Pre-treatment with phenobarbital did not change the fluoride values. Also in mice and rats, little or no skeletal deposition of fluoride ions did occur, suggesting low or no metabolism for isoflurane.

In miniature swine treated with subanesthetic doses, values indicated little or no metabolism of isoflurane.

In vitro studies confirmed the findings using livers from both untreated and phenobarbital pretreated mice and rats. When the liver homogenates were exposed to isoflurane, inorganic fluoride production was very low.

In three human volunteers given 0.9% (0.8 MAC) of isoflurane for an average of 2.8 hours, it was also found that the metabolism of isoflurane was low. The peaks occurred during the first

postanesthetic day; by the third day all values had returned to preanesthetic levels. Tonic fluoride levels in urine rose from around 100 mcM/day preanesthesia to a peak of around 400 mcM and had returned to baseline levels on the fourth postanesthetic day.

STORAGE AND STABILITY

Store between 15 °C and 30 °C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Isoflurane USP (Isoflurane, 99.9%) is packaged in 100 and 250 mL amber-coloured bottles.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

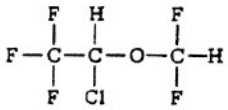
Drug Substance

Proper name: Isoflurane, USP

Chemical name: 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether

Molecular formula and molecular mass: $C_3H_2ClF_5O$ 184.50 g/mol

Structural formula:



Description: Isoflurane is a clear, colourless liquid having a slight odour. It is nonflammable and soda lime stable. Easily miscible with organic liquids including fats and oils. Insoluble in water. Boiling point is 48.5 °C (uncorrected).

Physicochemical properties:

Boiling point (at 760 mm Hg)	48.5 °C	
Refractive index n_D^{20}	1.2990 – 1.3005	
Specific gravity 25°/25°C	1.496	
Vapour pressure in mm Hg	18 °C	218
	20 °C	238
	22 °C	261
	24 °C	285
	26 °C	311

Equation for vapour pressure calculation:

$$\log_{10}P_{vap} = A + \frac{B}{T}$$

A = 8.056
B = -1664.58
T = °C + 273.16 (Kelvin)

Partition coefficients at 37 °C

Water/gas	0.61
Blood/gas	1.43
Oil/gas	90.8

DETAILED PHARMACOLOGY

Isoflurane is a halogenated methyl ethyl ether.

Human Data
The dose of epinephrine producing ventricular extrasystoles in 50 percent of humans anesthetized with 1.25 MAC isoflurane is 6.7 mcg per kg when the epinephrine is injected submucosally. This would equal 47 mL of a 1:100,000 epinephrine containing solution in a 70 kg man.

Isoflurane does not cause EEG spiking or convulsive activity either at high, normal or low levels of arterial PCO_2. Myoclonus or other muscular movement suggesting increased central nervous system hyperactivity is not provoked by isoflurane.

Animal Data
Isoflurane produces general anesthesia on inhalation in mice, dogs, monkeys, rabbits, and rats. The low blood/gas partition coefficient (1.4 for isoflurane compared to 1.9 for enflurane and 2.4 for halothane) permits a rapid induction of and recovery from anesthesia. Recovery is free from nausea, vomiting, or evidence of malaise.

MAC in dogs, the minimum alveolar concentration at which 50% of the animals move in response to pain stimulation, is 1.46%. The anesthetic index in dogs (dose at apnea divided by MAC) is 2.5. The anesthetic index for other anesthetics is: enflurane 2.0, halothane 2.9, cyclopropane 2.4, and diethyl ether 2.9.

In rats, isoflurane is favored in either of two anesthetic indices indicating margin of safety (see Table: Anesthetic Indices). The respiratory anesthetic index is the ratio of the brain anesthetic concentration at respiratory arrest/minimum brain anesthetic concentration producing anesthesia. The cardiac arrest index is the ratio of the myocardial anesthetic concentration at circulatory collapse/minimum heart anesthetic concentration at which anesthesia is produced.

Anesthetic Indices:

	Respiratory	Cardiac
ISOFLURANE	3.1	5.7
HALOTHANE	2.3	3.0
METHOXYFLURANE	2.2	3.7
ENFLURANE	1.8	3.3

Like other halogenated agents, isoflurane causes respiratory depression and respiratory acidosis in dogs, rats, rabbits, monkeys, and humans.

The arrhythmic doses of epinephrine in dogs anesthetized with isoflurane do not differ from those which produce arrhythmias in the awake animal.

TOXICOLOGY

Acute

A single acute study in 4 week old female mice given isoflurane intraperitoneally in olive oil yielded an LD_{50} of 6.74 g/kg (5.87 to 7.77). The animals showed disorientation and hypnosis; at the higher doses some showed convulsions.

Subacute and Chronic

Groups of five mature beagle dogs were exposed to 1.5 MAC of isoflurane, enflurane, halothane, methoxyflurane, nitrous oxide, or thiopental. There was a control group of five animals. Each group was exposed for four hours per day every other day, for a total of 16 hours of anesthesia. Histopathological examination of liver and kidney tissues showed no cellular damage related to the anesthetics. Serum creatinine, BUN and SGPT were normal. Urine lysozyme measurements revealed no consistent change in the lysozyme excretion, with no differences among the anesthetics. It was concluded from these results that there was no renal or hepatic toxic effect from isoflurane or any other anesthetic.

Five groups of five Rhesus monkeys were exposed for four hours per day on alternate days for a total of 16 hours of anesthesia. The anesthetic agents used were isoflurane (1.5 to 2.5%), enflurane (1.5 to 2.0%), methoxyflurane (0.5 to 0.7%), and halothane (1.0 to 1.25%). No other drugs were administered. No significant changes in serum creatinine, BUN or SGPT were found. The minimal changes found in liver and kidney tissues did not indicate that isoflurane was nephrotoxic or hepatotoxic.

The chronic toxicity of isoflurane was compared to that of halothane and diethyl ether in mice, rats, and guinea pigs. Animals were exposed continuously for 35 days to 0.05% or 1/30th MAC isoflurane. At the end of this period, all species showed no effect other than a slightly lower weight gain compared to controls. By comparison, halothane animals tolerated only 1/200th MAC, or 0.005% concentration. At concentrations higher than this, halothane exhibited focal hepatic necrosis and lipoidosis which was not seen in the animals exposed to isoflurane.

Human volunteers given isoflurane at 1 to 2 MAC for 6 to 7.5 hours did not show postanesthetic evidence of significant liver or renal impairment. BSP retention was slightly increased 24 hours following anesthesia although the values remained in the normal range. This result differed from the result obtained in similar tests with halothane or fluroxene; the latter agents increased BSP significantly above normal. Isoflurane did not significantly affect SGOT, SGPT or LDH. Isoflurane did not increase BUN or serum creatinine.

A 15 month chronic toxicity study was also carried out in Swiss ICR mice. Isoflurane, enflurane, halothane, methoxyflurane and nitrous oxide were used; air and oxygen were given to groups of control mice. The anesthetics were given at 1/2, 1/8 and 1/32 MAC for four exposures to the mothers during pregnancy, and for 24 exposures to the pups post-partum. The pups were followed to 15 months, at which time they were sacrificed and autopsied. No significant

differences were found between isoflurane treated animals and those exposed to halothane, enflurane, methoxyflurane or nitrous oxide.

Reproductive and Teratology

Reproduction studies, including fertility, general reproductive performance, teratogenicity, and lactation, did not show any abnormality in rats in concentration up to 2.34%.

The administration of 1.05% isoflurane to pregnant rats for 6 hours/day for 3 days during organogenesis, the administration of 1.63 – 1.73% isoflurane to pregnant rats for 1 hour/day for 5 days during organogenesis, and the administration of 2.28 – 2.34% isoflurane to pregnant rabbits for 1 hour/day for 4 days during organogenesis produced no fetotoxic effects. In contrast, the administration of isoflurane to pregnant mice has been shown to have a possible fetotoxic effect at anesthetic concentrations (0.6%) for 4 hours/day for 10 days during organogenesis. The relevance of these studies to the human is not known.

Studies in rodents demonstrate that the use of anesthetic agents during the period of rapid brain growth or synaptogenesis results in widespread neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis. Based on comparisons across species, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester through the first several months of life, but may extend out to approximately 3 years of age in humans.

In primates, three hours exposure to an anesthetic regimen that produced a light surgical plane of anesthesia did not increase neuronal cell loss; however, treatment regimens of five hours or longer increased neuronal cell loss.

Data in rodents and in primates suggest that the neuronal and oligodendrocyte cell losses are associated with subtle but prolonged cognitive deficits in learning and memory (see WARNINGS AND PRECAUTIONS, Special Populations).

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PART III: PATIENT MEDICATION INFORMATION

[Pr] Isoflurane USP

(Isoflurane, 99.9%)

Read this carefully before you start taking Isoflurane USP and each time you get a refill. This leaflet is a summary and will not tell you everything about Isoflurane USP. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about Isoflurane USP.

ABOUT THIS MEDICATION

What the medication is used for:
Isoflurane USP is used to put you under general anesthesia.

What it does:
Isoflurane USP is used to induce and maintain anesthesia.

When it should not be used:
Isoflurane USP should not be used if:

- You have been told that you are allergic to isoflurane or other inhaled general anesthetics, or components of the container.
- You have a history of liver inflammation (hepatitis) due to the use of an inhaled general anesthetic, or have experienced unexplained liver problems (for example jaundice with fever) after a previous use of an inhaled general anesthetic.
- You or any member of your family has experienced a condition called malignant hyperthermia (a genetic disorder that causes rapid raise in body temperature) during an operation.

What the medicinal ingredient is:
Isoflurane, USP

What the nonmedicinal ingredients are:
The finished product is composed solely of the active ingredient, isoflurane, USP.

What dosage forms it comes in:
Isoflurane USP (Isoflurane, 99.9%) is available in 100 mL and 250 mL amber-colored bottles. The liquid is changed to gas in a vaporizer for inhalation. The vaporizer is designed to be used only with Isoflurane USP.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Isoflurane USP should only be administered by qualified individuals trained in general anesthesia in an adequately equipped facility.**
- **Isoflurane USP may trigger a rise in blood potassium or body temperature. You may experience stiff muscles, changes in blood pressure, rapid breathing, a bluish colour to lips or fingers, rapid or irregular heart rate. Trained healthcare professionals will take care of you if this happens.**

You should talk to your anesthesia professional prior to your anesthesia if you are aware of any of the following conditions:

- You have been told that you are allergic to isoflurane or other inhaled general anesthetics, or components of the container.
- You have previously had general anesthesia, particularly if repeated over a short period of time.
- A doctor has difficulty placing a tube down your throat to help you breathe.
- You are pregnant (or may be pregnant).
- You are breast-feeding.
- You or a member of your family suffers from malignant hyperthermia (a genetic disorder that causes rapid raise in body temperature).
- You are suffering from any other illness, such as diabetes, severe headaches, cancer, problems with your nerves or muscles (especially muscular dystrophy), nausea, or vomiting.
- You have or are at risk for developing Increased Intracranial Pressure (ICP). ICP is increased pressure inside the skull with general symptoms such as headache, vomiting without nausea, altered level of consciousness, back pain, and changes to your eyesight.
- You have low blood pressure, heart, kidney, or liver problems.
- You are taking prescription or non-prescription medications or herbal medicines.

Recovery of consciousness following Isoflurane USP administration generally occurs within minutes. Change in mood may persist for several days following administration.

Performance of activities requiring mental alertness or coordination such as operating a motor vehicle or hazardous machinery may be impaired for some time after general anesthesia. Do not drive a motor vehicle or operate hazardous machinery for at least 24 hours after having a general anesthetic.

INTERACTIONS WITH THIS MEDICATION

Serious Drug Interactions

- Tell your healthcare professional if you have muscular diseases (especially muscular dystrophy), and:
  - You are taking potassium, and/or
  - You have heart problems, especially irregular heart beats

Tell your doctor, nurse or pharmacist about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Drugs that may interact with Isoflurane USP include:

- Other anesthetics, tranquillizers (e.g., benzodiazepines), narcotics (e.g., opioids), muscle relaxants (e.g., pancuronium), and nitrous oxide gas.
- Calcium channel blockers (e.g., used to treat high blood pressure or seizures)
- Beta blockers (e.g., used to treat high blood pressure and heart problems)
- Monoamine Oxidase (MAO) inhibitors (e.g., used to treat depression, anxiety and migraine)
- Isoniazid (a treatment for tuberculosis)
- Indirect-acting sympathomimetics (amphetamines and their derivatives, psychostimulants, appetite suppressants, ephedrine and its derivatives)
- Alcohol (chronic use before anesthesia)
- St. John's Wort

PROPER USE OF THIS MEDICATION

Usual Dose:
Your anesthesia provider will decide what dose of Isoflurane USP you will receive. The dose will vary depending on your age, weight, the type of anesthesia that you are having, and other factors.

Overdose:
Overdosage will be handled by the anesthesia provider.

In case of drug overdose (especially if you have accidentally come in contact with Isoflurane USP on your skin, in your eyes, by swallowing it or by breathing it in), contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects include headache, cough, fatigue, mood changes, and nightmare.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

After exposure to Isoflurane USP, you should contact your doctor or anesthesia provider if you have any of the following reactions:

Common	Agitation, Confusion
	Chills/Shivering
	Difficulty Breathing
	Increased Blood Sugar: frequent urination, thirst, and hunger
	Liver Disorders: yellow color to skin and eyes, dark urine
	Muscle Pain
	Nausea, Vomiting
	Nervous System Disorders: confusion, nervousness, abnormal gait, dizziness, drowsiness, intellectual function decreased
	Rash
	Slow, Rapid, or Irregular Heartbeat
	Weakness
Uncommon	High Blood Pressure: headache, altered vision, nausea, vomiting
	Low Blood Pressure: light-headedness, fainting, especially when getting up from a lying or sitting position
	Malignant Hyperthermia: sudden fever with stiffness, pain and weakness in your muscles
	Seizure or Fits
Frequency Unknown	Heart Attack: chest pain, shortness of breath, heart burn, sweating, weakness, fatigue, light-headedness, nausea

This is not a complete list of side effects. For any unexpected effects while taking Isoflurane USP, contact your doctor, anesthesia provider, or pharmacist.

HOW TO STORE IT

Isoflurane USP should only be administered in an adequately equipped facility. Isoflurane USP must be kept out of reach and sight of children. **It is stored between 15 °C and 30 °C.**

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about Isoflurane USP:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada.html); the Fresenius Kabi Canada Ltd. website (fresenius-kabi.ca), or by calling 1-877-821-7724.

This leaflet was prepared by:
Fresenius Kabi Canada Ltd.
165 Galaxy Blvd, Suite 100
Toronto, ON M9W 0C8

Last revised: May 23, 2018