

PRODUCT MONOGRAPH

**Pr ISOFLURANE<sup>®</sup>, USP**

isoflurane

Volatile Liquid  
> 99.9% isoflurane

Inhalation Anesthetic

Abbott Laboratories, Limited  
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St-Laurent, QC, Canada, H4S 1Z1

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**ISOFLURANE<sup>®</sup>**  
(isoflurane)

**PART I: HEALTH PROFESSIONAL INFORMATION**

**SUMMARY PRODUCT INFORMATION**

<b>Route of Administration</b>	<b>Dosage Form / Strength</b>	<b>Nonmedicinal Ingredients: None</b>
Inhalation	Volatile Liquid / > 99.9% isoflurane	ISOFLURANE <sup>®</sup> (isoflurane) is a clear, colourless, stable liquid containing no additives or stabilizers. The finished product only contains the active drug substance, isoflurane.

**INDICATIONS AND CLINICAL USE**

ISOFLURANE<sup>®</sup> (isoflurane) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

**Pediatrics (< 18 years of age):**

Isoflurane is not indicated in children.

**Geriatrics (> 65 years of age):**

For details, see **DOSAGE AND ADMINISTRATION**, **Recommended Dose and Dosage Adjustment**.

**CONTRAINDICATIONS**

ISOFLURANE<sup>®</sup> (isoflurane) is contraindicated in:

- patients with known sensitivity to isoflurane or the other halogenated agents
- patients in whom liver dysfunction, jaundice or unexplained fever, leucocytosis, or eosinophilia has occurred after a previous halogenated anesthetic administration (see **WARNINGS AND PRECAUTIONS**)
- patients with known or suspected genetic susceptibility to malignant hyperthermia, or in patients with a known or suspected history of malignant hyperthermia.
- patients when general anesthesia is contraindicated.

## **WARNINGS AND PRECAUTIONS**

### **General**

ISOFLURANE<sup>®</sup> (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.

Since levels of anesthesia may be altered easily and rapidly, only vaporizers which deliver predictable concentrations with reasonable accuracy should be used. Hypotension and respiratory exchange can serve as a guide to anesthesia depth. With deep levels of anesthesia, more marked hypotension and respiratory depression are encountered.

**ISOFLURANE<sup>®</sup> (isoflurane) potentiates all commonly used muscle relaxants; the effect being most profound with the non-depolarizing type.** Therefore, less than the usual amounts of such agents should be used. Neostigmine reverses the effects of nondepolarizing muscle relaxants, but has no effect on the relaxant properties of isoflurane.

Blood loss during abortion is increased when halogenated agents such as isoflurane are used for anesthesia.

The safety of repeated anesthesia with isoflurane has not been established.

### **Safe Use of 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<sup>®</sup>). When a clinician suspects that the CO<sub>2</sub> absorbent may be desiccated, it should be replaced before administration of isoflurane. The colour indicator of most CO<sub>2</sub> absorbents does not necessarily change as a result of desiccation. Therefore, the lack of significant colour 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.

### **Cardiovascular**

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

### **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 nonspecific features such as muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias and unstable blood pressure. (It should also be noted that many of these nonspecific signs might appear with light anesthesia, acute hypoxia, etc.).

An increase in overall metabolism may result 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. PaO<sub>2</sub> and pH may decrease, and hyperkalemia and a base deficit may appear. Treatment includes discontinuance of 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 derangement. Renal failure may appear later, and urine flow should be sustained if possible.

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.

### **Hepatic**

As with other halogenated anesthetics, isoflurane may cause sensitivity hepatitis in patients who have been sensitized by previous exposure to halogenated anesthetics (see **CONTRAINDICATIONS** and **ADVERSE REACTIONS**). Therefore, appropriate alternative anesthetic agent(s) should be considered, this is especially important in patients with pre-existing hepatic conditions.

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.

### **Neurologic**

Isoflurane may increase cerebral blood flow and hence cerebrospinal fluid pressure, and therefore should be used with special care in patients with elevated cerebrospinal fluid pressure. This effect on flow and pressure is reversed by hyperventilation.

Isoflurane, as well as other general anesthetics, may cause a slight decrease in intellectual

function for two or three days following anesthesia. As with other anesthetics, small changes moods and symptoms may persist for up to 6 days after administration. Patients should be advised that performance of activities requiring mental alertness, such as operating a motor vehicle or hazardous machinery, may be impaired for some time after general anesthesia.

### **Respiratory**

**Respiration must be closely monitored and supported when necessary.**

### **Special Populations**

**Pregnant Women:** Safe use in pregnancy has not been established. Reproduction studies have been performed in rats and mice after repeated exposures to anesthetic concentrations of isoflurane and have revealed no evidence of impaired fertility or harm to the fetus due to isoflurane. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

**Use in Caesarean Section:** Isoflurane, in concentrations up to 0.75%, has been shown to be safe and efficacious for the maintenance of anesthesia for caesarean section.

In a published study of patients undergoing Caesarean section, the most common adverse reactions in the mother during the first 72 postoperative hours were coughing and pharyngitis. No adverse outcomes were reported in either the mother or the newborn.

**Nursing Women:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when isoflurane is administered to a nursing woman.

### **Pediatrics (< 18 years of age):**

Isoflurane is not indicated in children.

### **Geriatrics: (> 65 years of age)**

As with other agents, lesser concentrations of isoflurane are normally required to maintain surgical anesthesia in elderly patients. (See **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment.**)

### **Monitoring and Laboratory Tests**

Bromsulphalein (BSP) retention is mildly elevated postoperatively in some cases. Elevated glucose and white blood cell counts have been observed intraoperatively. In diabetic patients, the possible exacerbation of hyperglycemia should be considered.

Transient decrease in serum cholesterol has also been observed.

## **ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

The following adverse reactions have been observed during ISOFLURANE<sup>®</sup> (isoflurane) administration.

- Malignant hyperthermia (see **WARNING AND PRECAUTIONS**)
- Hypotension and respiratory depression;
- Arrhythmias;
- Postoperative ileus, shivering, nausea and vomiting;
- Elevation of the white blood cell count (even in the absence of surgical stress);
- Delirium, hallucinations and hiccups.

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

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

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.

### **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.*

Induction of anesthesia with isoflurane in 20 unpremedicated patients was associated with

salivation (5), excitement (11), coughing or breath-holding (12), and laryngospasm (3).

The most common adverse events observed during the recovery from anesthesia in a clinical trial (N=100) are presented in **Table 1**.

Nausea	5%
Vomiting	3%
Excitement and delirium	6%
Muscle rigidity	26%
Shivering	62%

In one pivotal clinical trial (including 204 patients), shivering was seen in only 4 patients (2%) following surgery. Nausea and/or vomiting occurred in 12 of 71 males (17%) and in 37 of 133 females (28%). The overall incidence during the first 24 hours was 24% and, of these, one-third had recurrent symptoms.

### **Abnormal Hematologic and Clinical Chemistry Findings**

Transient increases in bromsulphalein (BSP) retention, blood glucose and serum creatinine with decrease in BUN, serum cholesterol and alkaline phosphatase have been observed.

Elevation of SGOT, LDH and bilirubin with or without jaundice have been reported in the post-operative period following isoflurane anesthesia in some patients.

Elevated glucose and white blood cell counts have been observed intraoperatively. In diabetic patients, the possible exacerbation of hyperglycemia should be considered.

## **DRUG INTERACTIONS**

### **Drug-Drug Interactions**

The action of nondepolarizing relaxants is augmented by isoflurane. Less than the usual amounts of these drugs should be used. If the usual amounts of nondepolarizing relaxants are given, the time for recovery from neuromuscular blockade will be longer in the presence of isoflurane than during anesthesia with halothane or a balanced technique.

### **Benzodiazepines and Opioids**

Benzodiazepines and opioids would be expected to decrease the MAC of isoflurane in the same manner as with other inhalational anesthetics.

## **Nitrous oxide**

As with other halogenated volatile anesthetics, the anesthetic requirement for isoflurane is decreased when administered in combination with nitrous oxide (see **DOSAGE AND ADMINISTRATION**).

## **Neuromuscular Blocking Agents**

As is the case with other volatile anesthetics, isoflurane increases both the intensity and duration of neuromuscular blockade induced by non-depolarizing muscle relaxants.

## **Drug-Food Interactions**

Increased blood solubility and uptake of the soluble anesthetics after eating prolong the rate of induction of anesthesia by slowing the rate of rise of the end-tidal (alveolar) concentration.

In a study of 12 healthy male volunteers, the isoflurane blood solubility was increased significantly ( $p < 0.01$ ) 30-45 minutes after eating. This increase was not statistically significant 1 hour after eating.

## **DOSAGE AND ADMINISTRATION**

### **Dosing Considerations**

#### **Preanesthetic Medication**

Preanesthetic medication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by ISOFLURANE<sup>®</sup> (isoflurane) and that the heart rate tends to be increased. The use of anticholinergic drugs is a matter of choice.

#### **Induction: Adult Patients**

Induction may be achieved using isoflurane alone, with oxygen or in combination with oxygen-nitrous oxide mixtures. Under these conditions coughing, breath-holding or laryngospasm may be encountered. If these difficulties are to be avoided, a hypnotic dose of an ultra-short-acting barbiturate should be used to induce unconsciousness, followed by the isoflurane mixture. It is recommended that once anesthesia has been induced with a short-acting barbiturate or other intravenous induction agent, administration of isoflurane may be initiated at a concentration of 0.5%.

In general, inspired concentrations of 1.5% to 3.0% isoflurane with 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.

The administration of general anesthesia must be individualized based on the patient's response.

## **Maintenance**

Surgical levels of anesthesia may be maintained with 1.0% to 2.5% isoflurane when 50% to 70% nitrous oxide is used concomitantly. An additional 0.5-1.0% isoflurane may be required when given with oxygen alone. If added relaxation is required, supplemental doses of muscle relaxants may be used.

The level of blood pressure during maintenance is an inverse function of isoflurane concentration in the absence of other complicating problems. Excessive decreases may be due to depth of anesthesia and in such instances should be corrected by lightening the level of anesthesia.

## **Recommended Dose and Dosage Adjustment**

See **Table 2** below for MAC values relative to age.

<b>Age of Patient</b>	<b>With 100% Oxygen</b>	<b>With 70% N<sub>2</sub>O</b>
26 ± 4 years	1.28%	0.56%
44 ± 7 years	1.15%	0.50%
64 ± 5 years	1.05%	0.37%

## **Elderly**

As with other agents, lesser concentrations of isoflurane are normally required to maintain surgical anesthesia in elderly patients.

## **Administration**

### **Administration Equipment**

ISOFLURANE<sup>®</sup> (isoflurane) should be administered only by persons trained in the administration of general anesthesia (see **WARNINGS AND PRECAUTIONS**).

The concentration of isoflurane being delivered from a vaporizer during anesthesia should be known. This may be accomplished by using a) flow-through vaporizers calibrated specifically for isoflurane b) vaporizers from which delivered flows can easily and readily be calculated.

The delivered concentration from such a vaporizer may be calculated:

$$\% \text{ isoflurane} = \frac{100 P_V F_V}{F_T (P_A - P_V)}$$

$P_A$  = Pressure of atmosphere  
 $P_V$  = Vapour pressure of isoflurane  
 $F_V$  = Flow of gas through vaporizer (mL/min)  
 $F_T$  = Total flow gas used (mL/min)

## **OVERDOSAGE**

Overdosage with ISOFLURANE<sup>®</sup> (isoflurane) will generally produce marked hypotension and apnea. In the event of overdosage, or what may appear to be overdosage, the following action should be taken:

1. Stop drug administration;
2. Establish that the airway is clear;
3. Instigate assisted or controlled ventilation with pure oxygen as the circumstances dictate.

## **ACTION AND CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

ISOFLURANE<sup>®</sup> (isoflurane), a halogenated methyl ethyl ether, is an inhalation anesthetic used in induction and maintenance of general anesthesia.

### **Pharmacodynamics**

Induction and recovery from isoflurane anesthesia are rapid due to its low solubility (blood/gas coefficient; 1:4). Isoflurane does not appear to stimulate excessive salivation or tracheo-bronchial secretions even though the pungency of isoflurane may limit the rate of induction. Pharyngeal and laryngeal reflexes are diminished quickly. The level of anesthesia with isoflurane changes rapidly, which would be predicted based upon its Oswald partition coefficients.

Isoflurane is a profound respiratory depressant. Isoflurane reduces ventilation as depth of anesthesia increases. This is a result of a decrease in tidal volume with rate of respiration remaining essentially constant. The respiratory depression is partially reversed by surgical stimulation, even at deeper levels of anesthesia. Isoflurane provokes a sigh response reminiscent of that seen with diethyl ether and enflurane.

There is a blood pressure decrease with induction of anesthesia, followed by a return to near normal with surgical stimulation. Increasing the depth of anesthesia correspondingly decreases blood pressure. Furthermore, nitrous oxide diminishes the inspired concentration of isoflurane required to reach a desired level of anesthesia and also has a favorable effect on the parameters of the anesthetic process.

With controlled ventilation and normal PaCO<sub>2</sub>, cardiac output tends to be maintained despite increasing depth of anesthesia, primarily through an increase in heart rate, which compensates for a reduction in stroke volume.

With spontaneous respiration, the resulting hypercapnea may further increase heart rate and raise cardiac output above awake levels.

The cardiac rhythm during isoflurane anesthesia is stable. Isoflurane has not been shown to sensitize the myocardial conduction system to epinephrine and does not produce serious arrhythmias in animals.

Limited data from studies in man indicates that injection subcutaneously of 0.25 mg of epinephrine (50 mL of 1:200,000 solution) does not cause ventricular arrhythmias in patients anaesthetized with isoflurane. It should be noted that doubling this dose will produce ventricular extrasystoles in about half of patients anesthetized with 1.25 MAC (Minimum Alveolar Concentration) isoflurane.

Muscle relaxation in man is adequate for intra-abdominal operations at normal levels of anesthesia. All commonly used muscle relaxants are compatible with isoflurane.

Should greater relaxation or complete paralysis be necessary, small doses of muscle relaxants may be used. Isoflurane potentiates all commonly used muscle relaxants, the effect being most profound with nondepolarizing relaxants.

Neostigmine reverses the effects of non-depolarizing muscle relaxants in the presence of isoflurane but has no effect on the relaxant properties of isoflurane itself.

The systemic metabolism of isoflurane in humans was studied in 189 patients. The fluoride levels observed indicated that isoflurane given at 0.7% concentration for 178 minutes is not subject to enzymatic degradation processes that release fluoride into the blood.

In other studies, relatively little metabolism of isoflurane occurred in the human body. The low fluoride levels are not considered likely to produce impairment of renal function.

Isolated cases of convulsions have been reported in patients receiving isoflurane. In general, isoflurane produces an EEG pattern similar to that seen with other volatile anesthetics.

### **Pharmacokinetics**

A clinical trial evaluating the pharmacokinetics of inhaled anesthetics on 48 patients (16 patients received isoflurane) demonstrated that the median steady state volume of distribution of isoflurane is in average 4285 (range of 1509-9640) mL<sub>vapour</sub> kg<sub>bw</sub><sup>-1</sup>. The median transport clearance from the central to the peripheral compartment for isoflurane is 30.7 (range of 15.9-38.7) mL<sub>vapour</sub> kg<sub>bw</sub><sup>-1</sup> min<sup>-1</sup>.

**Solubility:** Partition coefficients at 37°C are as follows:

Water/ gas	0.61
Blood/ gas	1.43
Oil/ gas	90.80

**Metabolism:** Relatively little metabolism of isoflurane occurs in the human body. In the postoperative period, of the isoflurane taken up, only 0.2-1% can be recovered as urinary metabolites. Peak serum inorganic fluoride values usually average less than 5 micromole/litre and occur about four hours after anesthesia, returning to normal levels within 24 hours. No signs of renal injury have been reported after isoflurane administration.

### **Special Populations and Conditions**

**Geriatrics:** For details, see **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**.

**Hepatic Insufficiency:** For details, see **WARNINGS AND PRECAUTIONS, Hepatic**.

### **STORAGE AND STABILITY**

Store between 15°C to 25°C. ISOFLURANE® (isoflurane) contains no additives.

### **DOSAGE FORMS, COMPOSITION AND PACKAGING**

ISOFLURANE® (isoflurane) is packaged in 100 mL and 250 mL amber-colored bottles.

ISOFLURANE (isoflurane) is a non-flammable inhalation anesthetic agent that is a clear, colourless, stable liquid whose purity exceeds 99.9%. The finished product is comprised only of the active drug substance, isoflurane.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

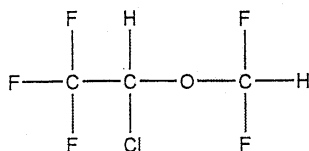
Proper name: isoflurane

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

Molecular formula: C<sub>3</sub>H<sub>2</sub>ClF<sub>5</sub>O

Molecular mass: 184.50

Structural formula:



Physicochemical properties:

Isoflurane is a nonflammable inhalation anesthetic agent. The boiling point is 47-50°C at 760 mmHg, and the vapor pressure (in mmHg) is 238 at 20°C, 295 at 25°C, 367 at 30°C and 450 at 35°C.

Vapor pressures can be calculated using the equation:

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

$$A = 8.056, B = -1664.58, T = ^\circ\text{C} + 273.16 \text{ (Kelvin)}$$

The specific gravity is 1.496 at 25°C.

The refractive index at 20°C is 1.2990-1.3005. The blood/gas coefficient is 1.43 at 37°C and the oil/gas coefficient is 97.8 at 37°C.

Isoflurane is a clear, colorless, stable liquid whose purity exceeds 99.9%. No stabilizers are added as these have been found, through controlled laboratory tests, to be unnecessary. The partition coefficients of isoflurane at 23°C are 62.0 in conductive rubber and 110 in polyvinyl chloride.

## DETAILED PHARMACOLOGY

### Animal Pharmacology

As shown by the studies in mouse, rat, dog and rabbit, isoflurane produced a state of general anesthesia on inhalation. Anesthesia of varying depths was produced depending on the dose administered. In general, the anesthesia was characterized by rapid induction with very little salivation, good maintenance and rapid recovery. Recovery was readily affected by discontinuation of isoflurane administration. Relaxation was good, some analgesia was present. The recovery time was dependent on the dose, duration of anesthesia, and the individual animal or animal species. Nausea or vomiting was rare if not absent in dog and rabbits after single or repeated anesthesia.

The minimum alveolar concentration (MAC) of anesthetic preventing movement in 50% of the animals in response to a painful stimulus was determined in ten dogs and the value was found to be 1.46%.

In several studies, dogs anaesthetized with isoflurane at varying exposure times showed physiologically similar effects to halothane and enflurane, but markedly fewer arrhythmias occurred with isoflurane.

Compatibility of isoflurane with epinephrine was assessed by intravenous injection of 10 microg/kg of epinephrine to dogs. The heart was much less sensitive to the arrhythmic effect of epinephrine under isoflurane anesthesia than under halothane. If ventricular fibrillation occurred, the heart was defibrillated and the ability of the beta-adrenergic blocking agent, propranolol, to protect the myocardium against further epinephrine challenge, was assessed by the I.V. injection of 0.5 mg/kg. Propranolol was effective during anesthesia with isoflurane in protecting the myocardium against epinephrine.

Isoflurane produced a negative inotropic effect on the isolated papillary muscle of the cat, causing a work dependent decrease in maximal velocity, peak force, power, and work. Isoflurane altered the contractile state, affecting the cardiac muscle's ability to develop force and shorten. As a result of the study, it was judged that isoflurane was the least myocardial depressant of the group - halothane and isoflurane.

In a final study on cardiovascular effects, halothane and isoflurane inhibited phenylephrine induced contraction of isolated rat aorta in a dose-dependent manner, confirming their cardio-depressive action on smooth muscle.

Isoflurane was administered to thirteen healthy cats with implanted recording electrodes in the brain. Anesthetic concentration was varied and depths to create synchronous spike discharges were reached. Rarely was there motor activity.

Recovery was smooth and uneventful. It was concluded that isoflurane was a fast acting, potent anesthetic with desirable attributes for anesthesia. The electroencephalographic pattern was distinct.

Studies in dogs indicated that isoflurane does not cause EEG spiking or convulsive activity either at high, normal or low levels of arterial PCO<sub>2</sub>. Twitching or other muscular movement suggesting increased central nervous system hyperactivity is not provoked by isoflurane.

The metabolism of isoflurane by the enzymatic system has been studied in rat and miniature swine.

Metabolic studies have shown that isoflurane is only minimally metabolized when compared with other common anesthetic agents. The amount of isoflurane extracted or metabolized by the liver of three miniature swine exposed to this product over periods of from 20 hours to one week was found to be less than 2% confirming the very low biotransformation of this agent. Other studies, in rats with repeated exposure to sub-anesthetic levels of the agent, suggest that isoflurane is less toxic than other halogenated agents (methoxyflurane).

## **TOXICOLOGY**

### **Acute Toxicity**

**Mouse:** The LD<sub>50</sub> in mice by intraperitoneal injection of isoflurane in olive oil was found to be 6.74 g/kg at 24 hours. The animals showed disorientation and hypnosis. Convulsions occurred at higher doses.

### **Long-Term Toxicity**

Long-term effects on various organ systems were studied in dogs, monkeys, rats, mice, rabbits and guinea pigs.

**Mice:** A group of 48 mice were anesthetized with 0.015 - 0.15% isoflurane for a total of 35-day. Slower weight gains, and some small liver lesions were the only effects. In a similar study, 31 mice receiving 0.15 - 0.30% isoflurane for 21 days showed no auto- or cross-tolerance build-up to isoflurane anesthesia.

**Rats/Guinea Pigs:** The animals were placed in large plastic bags containing 0.015%, 0.05% and 0.15% isoflurane for a 35-day total exposure. Slower weight gains and small liver lesions were the only effects; no other histopathological effects were noted.

**Rabbits:** Five New Zealand white rabbits were anaesthetized with 0.75% isoflurane for 3 hours for 5 consecutive days. Histopathological studies revealed fatty infiltration of the kidneys but no liver or lung tissue abnormalities.

**Dogs:** In four separate studies, Beagle dogs were exposed to isoflurane 1.0 - 3.0% concentration for 2 - 3 hours per days for 4 days. With the exception of one study where kidney and liver exhibited slight fatty deposits, all other studies showed normal blood, urine, kidney and liver results.

**Monkeys:** Two groups of 5 Rhesus monkeys each were anaesthetized with 1.0 - 2.5% isoflurane for 4 hours per day for 4 days. Blood results were within normal limits; in some cases, kidney, liver and lung exhibited minute traces of fatty deposits. The minimal changes found in liver and kidney tissues did not indicate that isoflurane was nephrotoxic or hepatotoxic.

### **Other Toxicity**

Hepatic/Renal toxicity studies were performed on dogs receiving a maximum of 2.25% isoflurane for 4-6 hours. Blood and liver results were normal but fatty deposits were seen in kidney histological sections.

### **Carcinogenicity**

In carcinogenicity studies with 432 Swiss ICR mice and 330 CDBR rats, no tumourigenicity was evident with long-term exposure.

### **Mutagenicity**

Mutagenicity studies using rat and hamster tissue were performed by the Ames test and the sister-chromatid exchange test. Results indicate that isoflurane is not mutagenic.

### **Reproduction and Teratology**

A study designed to evaluate the effects of isoflurane upon reproduction performance in rats was conducted. Test animals were subjected to inhalation of test material vapor at a concentration of 0.15% or 0.60% for 2 hours daily on each of 14 days prior to mating. Control animals were subjected to chamber air.

Isoflurane exhibited no deleterious effects upon pre-implantation development or implantation itself. Fertility indices, litter sizes and early resorptions - all measures of possible early problems - were comparable to control values.

Teratogenicity studies on 60 rats and 30 mice (gestation day 6-15) with isoflurane exposure of 2 hours per day for 10 days showed no major abnormalities. Fetuses were normal. No visceral or skeletal defects due to exposure were detected. At higher doses, depression of growth rate was noted (0.4% isoflurane in rats) and resorption rates increased (0.3% isoflurane in mice).

Peri-post-natal studies on 20 rats (gestation day 15-20) were conducted using 0.1-0.4% isoflurane for 2 hours per day for 6 days. No female rats showed any ill-effects.

No treatment related effects were observed on litter numbers, pup weights, appearance, growth rates or survival to weaning.

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## PART III: CONSUMER INFORMATION

### Pr ISOFLURANE® (isoflurane)

This leaflet is part III of a three-part "Product Monograph" published when ISOFLURANE® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ISOFLURANE®. Contact your doctor or pharmacist if you have any questions about the drug.

#### ABOUT THIS MEDICATION

##### What the medication is used for:

ISOFLURANE® is used as a general anesthetic during surgery.

##### What it does:

ISOFLURANE® causes unconsciousness, muscle relaxation, and loss of sensation over the entire body so that surgery can be performed.

##### When it should not be used:

ISOFLURANE® should not be used in patients who:

- are allergic to isoflurane or other halogenated agents
- have experienced liver problems, jaundice, unexplained fever, or certain types of inflammation reactions after a previous halogenated anesthetic administration
- have been told by their doctors that they are genetically susceptible to a dangerously high body temperature when given some drugs used for general anesthesia (malignant hyperthermia MH).

##### What the medicinal ingredient is:

isoflurane

##### What the important nonmedicinal ingredients are:

The finished product is composed solely of the active ingredient, isoflurane.

##### What dosage forms it comes in:

ISOFLURANE® is available as a 99.9% pure volatile liquid in 100 mL and 250 mL amber coloured bottles.

#### WARNINGS AND PRECAUTIONS

BEFORE you undergo general anesthesia, tell your anesthesia professional if:

- you have kidney or liver problems
- you are pregnant or nursing
- you are allergic to isoflurane
- you are susceptible to malignant hyperthermia (MH)
- a doctor has difficulty placing a tube down your throat to help you breathe
- you are taking prescription or non-prescription

medications or herbal medicines.

Performance of activities requiring mental alertness, such as operating a motor vehicle or hazardous machinery, may be impaired for up to six days after general anesthesia. Wait 6 days and use caution before resuming these activities.

As with other anesthetics, small changes in moods may persist for several days following administration.

#### INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with ISOFLURANE® include the:

Benzodiazepines (Valium, Versed)  
Opioids (Morphine, Codeine)

#### PROPER USE OF THIS MEDICATION

##### Usual dose:

The proper dose is determined by a doctor trained in the administration of general anesthesia.

#### SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Common side effects include: shivering, nausea, and vomiting.

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

After exposure to ISOFLURANE®, you should immediately contact your physician or anesthesia professional if you have any of the following reactions:

Symptoms of malignant hyperthermia: sudden fever with stiffness, pain and weakness in your muscles

Symptoms of low blood pressure: dizziness/fainting

Difficulty breathing

Irregular heartbeats

A lack of passage of material through the bowel, with signs of abdominal pain, vomiting, shivering, nausea and constipation

Sudden confusion or lack of ability to pay attention and/or focus

Hallucinations

Hiccups

Jaundice (yellowing of the skin and/or eyeballs)

Symptoms of elevated rise in blood sugar: confusion, increased hunger and/or thirst, increased frequency of urination, fruity breath.

Isolated cases of seizures [(i.e., loss of consciousness with uncontrollable shaking ("fit"))].

*This is not a complete list of side effects. For any unexpected effects after receiving ISOFLURANE®, contact your doctor or pharmacist.*

## HOW TO STORE IT

ISOFLURANE<sup>®</sup> should be stored between 15°C and 25°C.

### **REPORTING SUSPECTED SIDE EFFECTS**

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

By toll-free telephone: 866-234-2345

By toll-free fax: 866-678-6789

On-line: [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)

By email: [CanadaVigilance@hc-sc.gc.ca](mailto:CanadaVigilance@hc-sc.gc.ca)

By regular mail:

Canada Vigilance National Office  
Marketed Health Products Safety and  
Effectiveness Information Division  
Marketed Health Products Directorate  
Health Products and Food Branch  
Health Canada  
Tunney's Pasture, AL 0701C  
Ottawa ON K1A 0K9

*NOTE: Before contacting Canada Vigilance, you should contact your physician or pharmacist.*

## MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:

<http://www.abbott.ca>

or by contacting the sponsor, Abbott Laboratories, Limited, at:  
1-800-699-9948.

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