

# INFORMATION FOR HEALTH PROFESSIONALS

## DATA SHEET

### ISOFLURANE

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#### **Presentation**

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A clear, colourless, volatile, non-flammable liquid for general inhalation anaesthesia.

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#### **Uses**

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#### *Actions*

ISOFLURANE is a halogenated volatile anaesthetic which induces and maintains general anaesthesia by depression of the central nervous system and resultant loss of consciousness.

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#### **Pharmacokinetics**

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The pharmacokinetics of ISOFLURANE are those of inhaled gaseous or volatile anaesthetics for which blood concentrations are related to alveolar concentrations through the established partition coefficients, and the distribution to tissues is also determined by solubility coefficients which are relatively constant under a wide variety of circumstances. ISOFLURANE shows very low solubility in blood and body tissues, much lower than for enflurane and halothane, thus its partial pressure (concentration) in alveolar gas or arterial blood rises to 50% of the inspired partial pressure (concentration) within 4-8 minutes of the start of its inhalation, and to 60% within 15 minutes. This rate of rise is slightly faster than that obtained with enflurane (a structural isomer of ISOFLURANE) and considerably faster (40%) than the more soluble halothane. Age significantly affects blood-gas partition coefficients for all anaesthetics; the lower blood-gas partition coefficients in children explain in part the more rapid increase in alveolar anaesthetic partial pressures in this group.

Throughout maintenance of anaesthesia, a high proportion of the ISOFLURANE inspired is eliminated by the lungs. When administration is stopped and inspired concentration becomes zero, the bulk of the remaining ISOFLURANE is eliminated unchanged from the lungs. In keeping with its low solubility, recovery from ISOFLURANE anaesthesia in man is rapid.

Biotransformation of ISOFLURANE is significantly less than that of enflurane or halothane. Humans and animals biotransform a small fraction of ISOFLURANE administered. In man about 0.2% administered is evident as recoverable metabolites (fluoride and organic fluorine), with approximately 50% of these excreted in the urine, the principal metabolite being trifluoroacetic acid. Enzyme induction associated with pre-existing drug therapy would not appear to be an important factor in the metabolism of ISOFLURANE in man, mainly because the overall metabolism of ISOFLURANE is so low.

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## **Indications**

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General anaesthetic for use in patients of all ages.

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## **Dosage And Administration**

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ISOFLURANE has a slight pungent ethereal odour, which may limit the rate of gas induction but, despite this, induction and particularly recovery are rapid. Salivation and tracheo-bronchial secretions may be stimulated in children but pharyngeal and laryngeal reflexes are quickly diminished. The use of ISOFLURANE-specific vaporisers will facilitate accurate control of the administered concentration of anaesthetic.

### ***Pre-medication:***

Pre-medication drugs should be selected according to the needs of the patient. The ventilatory depressant effect of ISOFLURANE should be taken into account. As ISOFLURANE causes increased heart rate and only weak stimulation of secretions, the use of anticholinergic drugs is a matter of choice.

### ***Induction:***

As ISOFLURANE has a mild pungency, inhalation should usually be preceded by the choice of a short-acting barbiturate, or other intravenous induction agent, to prevent coughing. Salivation and coughing may be troublesome in small children induced with Isoflurane. Alternatively, ISOFLURANE with oxygen or an oxygen/nitrous oxide mixture may be administered. It is recommended that induction with ISOFLURANE be initiated at a concentration of 0.5%. Concentrations of 1.5-3.0% usually produce surgical anaesthesia in 7-10 minutes.

Blood pressure decreases during induction but this may be compensated by surgical stimulation.

### ***Maintenance:***

Adequate anaesthesia for surgery may be sustained with an inspired ISOFLURANE concentration of 1.0% - 2.5% in an oxygen/70% nitrous oxide mixture. Additional inspired ISOFLURANE (0.5% - 1%) will be required with lower nitrous oxide levels, or when ISOFLURANE is given with oxygen alone or air/oxygen mixtures.

Blood pressure decreases during maintenance anaesthesia in relation to the depth of anaesthesia. That is, blood pressure is inversely related to the ISOFLURANE concentration. Provided there are no other complicating factors this is probably due to peripheral vasodilation.

Cardiac rhythm remains stable. Excessive falls in blood pressure may be due to the depth of anaesthesia and in such circumstances can be corrected by reducing the inspired ISOFLURANE concentration.

Induced hypotension can be achieved by artificially ventilating patients with ISOFLURANE 2.5-4.0%. Pre-treatment with clonidine significantly decreases the ISOFLURANE requirement for maintaining induced hypotension.

***Recovery:***

The concentration of ISOFLURANE can be reduced to 0.5% at the start of closing the operation wound, and then to 0% at the end of surgery, provided that the anaesthesiologist is satisfied that the effect of any neuromuscular blocking drugs has been reversed and the patient is no longer paralysed.

After discontinuation of all anaesthetics, the airways of the patient should be ventilated several times with oxygen 100% until complete recovery.

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## **Contraindications**

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Known sensitivity to ISOFLURANE or to other halogenated agents, especially patients with known or suspected susceptibility to malignant hyperthermia.

ISOFLURANE must not be used in patients who have developed an icterus and/or fever of unknown origin after administration of ISOFLURANE or another halogenated anaesthetic.

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## **Warnings And Precautions**

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ISOFLURANE is a profound respiratory depressant, this effect being accentuated by narcotic premedication or concurrent use of other respiratory depressants.

ISOFLURANE causes an increase in cerebral blood flow at deeper levels of anaesthesia (1.5%); this may give rise to an increase in cerebral spinal fluid pressure. Where appropriate, this can be prevented or reversed by hyperventilating the patient before or during anaesthesia.

As with other halogenated anaesthetics, ISOFLURANE must be used with caution in patients with increased intracranial pressure. Again, in such cases, hyperventilation may be necessary.

ISOFLURANE is a powerful systemic and coronary arterial dilator. The effect on systemic arterial pressure is easily controlled in the normal healthy patient and has been used specifically as a means of inducing hypotension. However, the phenomenon of "coronary steal" means that ISOFLURANE should be used with caution in patients with coronary artery disease. In particular, patients with subendocardial ischaemia might be anticipated to be more susceptible.

As with all general inhalation anaesthetics, it is advisable to allow 24 hours from recovery to elapse before driving or operating machinery.

Because levels of anaesthesia can be altered easily and quickly with ISOFLURANE, only vaporisers which produce a predictable concentration with a good degree of accuracy should be used. The degree of hypotension and ventilatory depression may provide some indication as to the level of anaesthesia. The level of anaesthesia may be changed quickly with ISOFLURANE. Heart rhythm remains stable but spontaneous breathing should be monitored closely and supported where necessary.

Salivation and tracheo-bronchial secretions may be stimulated in children but pharyngeal and laryngeal reflexes are quickly diminished.

It is recommended that vapour from this and other inhalational gases are efficiently extracted from the area of use.

As with all halogenated anaesthetics, repeat anaesthesia within a short period of time should be approached with caution since the risk of hepatotoxicity is not fully understood. There is insufficient experience of use in repeated anaesthesia to make a definite recommendation in this regard.

Caution should be exercised with administering ISOFLURANE to patients with pre-existing liver disease.

Although peak inorganic fluoride concentrations which result from the breakdown of ISOFLURANE are generally much lower than those considered to be nephrotoxic, no information is available on levels in patients with compromised renal function. The drug should therefore be used with extreme caution in these patients, or in those receiving nephrotoxic drugs concomitantly.

ISOFLURANE has been reported to interact with dry carbon dioxide absorbents during closed circuit anaesthesia, to form carbon monoxide. Inhalation of carbon monoxide may lead to formation of significant levels of carboxyhaemoglobin in exposed patients.

Carboxyhaemoglobin is toxic even in low concentrations and is not easily detected by standard anaesthesia monitors such as pulse oximeters. Direct measurement of carboxyhaemoglobin should be carried out in the event that a patient on closed circuit anaesthesia with an implicated agent develops oxygen desaturation which does not respond to the usual therapeutic measures.

Use of inhaled anaesthetic agents has been associated with very rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in children during the postoperative period. The condition has been described in patients with latent as well as overt neuromuscular disease, particularly Duchenne muscular dystrophy. Use of suxamethonium has been associated with most, but not all of these cases. These patients showed evidence of muscle damage with increased serum creatine kinase concentration and myoglobinuria. These patients did NOT have classical signs of malignant hyperthermia such as muscle rigidity, rapid increase in body temperature, or increased oxygen uptake and carbon dioxide

production. Prompt and vigorous treatment for hyperkalaemia and arrhythmias is recommended. Subsequent evaluation for latent neuromuscular disease is indicated.

***All necessary precautions should be taken to ensure that carbon dioxide absorbents are not allowed to dry out.***

#### **Use during Pregnancy and Lactation:**

Category B3.

Reproduction studies have been carried out on rats and rabbits after repeated exposure to ISOFLURANE at anaesthetic concentrations. In both species there was no effect on fertility,

pregnancy or delivery. The viability of offspring was unaffected and there was no evidence of teratogenicity. It is not known whether the consequences for humans are the same.

There is an increasing volume of information on the use of ISOFLURANE in pregnancy and obstetric anaesthesia but, with the exception of Caesarean section, the place of ISOFLURANE is still under development. A suitable level of anaesthesia for Caesarean section can be maintained with 0.5 - 0.75% ISOFLURANE in oxygen/nitrous oxide.

Increased blood loss has been observed, comparable with other inhalation anaesthetics (e.g. halothane), in patients undergoing induced abortions.

Should ISOFLURANE be administered during lactation, lactation is to be interrupted after the anaesthesia. Lactation can be restarted after the drug has been discharged from the circulation.

(See also INTERACTIONS)

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### **Adverse Effects**

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Adverse reactions encountered with ISOFLURANE are similar to those observed with other halogenated anaesthetics; these are hypotension, respiratory depression and arrhythmias.

Other minor side-effects encountered while using ISOFLURANE are an increase in the white blood cell count (even in the absence of surgical stress) and also shivering, nausea and vomiting during the post-operative period. These side-effects are observed in a similar proportion of patients to other anaesthetics.

During marketing, there have been rare reports of mild, moderate and severe (some fatal) post-operative hepatic dysfunction. The causal relationship is unknown.

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### **Interactions**

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ISOFLURANE produces sufficient muscle relaxation for some intra-abdominal operations. ISOFLURANE is compatible with all commonly used muscle relaxants, the effects of which may be markedly potentiated by ISOFLURANE. The effect is most notable in non-depolarising agents, thus lower doses would be used in the presence of ISOFLURANE. The effect of non-depolarising muscle relaxants can be counteracted by administering neostigmine as this has no effect on the relaxant properties of ISOFLURANE.

***Adrenaline:***

Administration of adrenaline by any route, and some other  $\beta$ -sympathomimetic drugs, may cause arrhythmias during ISOFLURANE anaesthesia.

***Calcium Antagonists (and other vasodilators):***

ISOFLURANE can cause marked hypotension in patients receiving concomitant therapy with calcium antagonists, especially those of the dihydropyridine class, (e.g. nifedipine, felodipine, amlodipine, isradipine). Patients receiving chronic therapy with other vasodilators such as ACE-inhibitors (e.g. captopril, enalapril, lisinopril) or  $\alpha_1$ -adrenoceptor antagonists (e.g. prazosin), may show unpredictable hypotension **with any type of anaesthesia.**

***Narcotic Analgesics:***

The anaesthetic effect of ISOFLURANE can be potentiated by narcotic analgesics.

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## **Overdosage**

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(See also PRECAUTIONS)

Overdosing with ISOFLURANE will result in marked depression of breathing, and a marked decrease in blood pressure, the latter being predominantly due to a peripheral vasodilatation rather than direct myocardial depression.

If it appears an overdose has been administered, stop drug inspiration immediately, establish a clear airway and initiate controlled ventilation with pure oxygen.

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## **Pharmaceutical Precautions**

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ISOFLURANE is fully compatible with other anaesthetic gases and volatile agents, but should be mixed and administered using agent-specific vapourising equipment.

Special precautions for storage: Room temperature (15 to 30°C). Keep container well closed.

Shelf-life as presented in 100 mL or 250 mL bottle: 5 years. Shelf-life (after first opening of container): If the container is left open, contents will evaporate. If securely reclosed, shelf-life is unaffected. Shelf-life after dilution or reconstruction is not applicable.

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## Medicine Classification

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Prescription Medicine

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## Package Quantities

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Bottles of 100 or 250 mL

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## Further Information

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Isoflurane is a colourless non-flammable general inhalation anaesthetic which contains no additive or stabiliser. It is 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether and has the structural formula:

Some physical constants of Isoflurane are:-

Molecular weight	184.5
Boiling point °C at 760 mm Hg	48.5
Specific gravity at 25 °C	1.496
Refractive index $n^{20}_D$	1.2990 - 1.3005

Vapour pressure mm Hg:

at 20°C	238
at 25°C	295
at 30°C	367
at 35°C	450

Partition coefficients at 37°C

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

Partition coefficients at 25°C for rubber and plastics:

Polyolefin/gas	ca 1.1
Polyurethane/gas	ca 1.4

Polyethylene/gas	ca 2.0
Butylacetate/gas	ca 2.5
Conductive rubber/gas	62.0
Butyl rubber/gas	75.0
Polyvinylchloride/gas	110.0

Flammability in oxygen or nitrous oxide:

at 9 joules/sec and 23°C

Non-flammable

at 900 joules/sec and 23°C

Non-flammable at anaesthetic concentrations.

The MAC (Minimum Alveolar Concentration), the standard measure of potency for anaesthetics, is 1.15% for middle-aged humans. There is an age-relationship, and the MAC is significantly higher in children.

<i>MAC AGE</i>	<i>Average Conc. in Oxygen</i>
up to 12 months	1.60 to 1.85%
1 to 5 years	1.50 to 1.60%
mid-twenties	1.25 to 1.30%
mid-forties	1.10 to 1.20%
mid-sixties	1.00 to 1.10%

**Stability:**

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|--------------------------------|--------------------|
| 1. UV light - 30 hours         | Stable (No change) |
| 2. Indirect sunlight - 3 years | Stable (No change) |

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**Name And Address**

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