SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

ISOFLURANE 100% Inhalation vapour, liquid

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Isoflurane, 100% active

3 PHARMACEUTICAL FORM

Inhalation vapour, liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Isoflurane is general inhalation anaesthetic for use in induction and maintenance.

4.2 Posology and method of administration

Posology

MAC values for Isoflurane vary with age. The table below indicates average MAC values for different age groups.

ADULTS*		
AGE	**Average MAC value**	
	In 100% Oxygen	**70% N2O**
26 ± 4 years	1.28%	0.56%
44 ± 7 years	1.15%	0.50%

64 ± 5 years	1.05%	0.37%
PAEDIATRIC POPULATION		
Age	**Average MAC Value in 100% Oxygen**	
Preterm neonates < 32 weeks gestational age	1.28%	
Preterm neonates 32-37 weeks gestational age	1.41%	
0-1 month	1.60%	
1-6 months	1.87%	
6-12 months	1.80%	
1-5 years	1.60%	

Premedication: Premedication drugs should be selected according to the needs of the patient. The respiratory depressant effect of Isoflurane should be taken into account. The use of anticholinergic drugs is a matter of choice, but may we advisable for inhalation induction in paediatrics.

Induction: As Isoflurane has a mild pungency, inhalation should usually be preceded by the use of a short acting barbiturate, or other intravenous induction agent, to prevent coughing. Alternatively, Isoflurane with oxygen or with 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.

Induction of anaesthesia in children:

Isoflurane is not recommended for use as an inhalation induction agent in infants and children because of the occurrence of cough, breath-holding, desaturation, increased secretions and laryngospasm (see section 4.4).

Maintenance: Adequate anaesthesia for surgery may be sustained with an inspired Isoflurane concentration of 1.0% to 2.5% in an oxygen/nitrous oxide mixture. Additional Isoflurane (0.5% to 1.0%) may be required when Isoflurane is given with oxygen alone.

For caesarean section, 0.5-0.75% isoflurane in a mixture of oxygen/nitrous oxide is suitable to maintain anaesthesia for this procedure.

Arterial pressure levels during maintenance tend to be inversely related to alveolar Isoflurane concentration in the absence of other complicating factors. Provided there are no other complicating factors this is probably due to peripheral vasodilation. 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.

Elderly: As with other agents, lesser concentrations of isoflurane are normally required to maintain surgical anaesthesia in elderly patients. See above for MAC values related to age.

Method of Administration:

Vaporisers specially calibrated for Isoflurane should be used so that the concentration of anaesthetic can be accurately controlled.

Isoflurane is not recommended as an induction agent in children.

4.3 Contraindications

Isoflurane is contraindicated in patients with known sensitivity to Isoflurane or to other halogenated anaesthetics.

It is also contraindicated in patients with known or suspected genetic susceptibility to malignant hyperthermia.

4.4 Special warnings and precautions for use

Vaporisers specially calibrated for isoflurane should be used so that the concentration of anaesthetic delivered can be accurately controlled.

Hypotension and respiratory depression increase as anaesthesia is deepened.

Reports of QT prolongation, associated with torsade de pointes (in exceptional cases, fatal), have been received. Caution should be exercised when administering isoflurane to patients at risk for QT prolongation.

Caution should be exercised in administering general anaesthesia, including isoflurane, to patients with mitochondrial disorders.

Isoflurane, like other inhalational agents, has relaxant effects on the uterus with the potential risk for uterine bleeding. Clinical judgement should be observed when using isoflurane during obstetric anaesthesia. Consideration should be taken to use the lowest possible concentration of isoflurane in obstetrical operations (please refer to section 4.6).

Isolated cases of increased carboxyhaemoglobin have been reported with the use of halogenated inhalation agents with a –CF2H moiety (i.e., desflurane, enflurane and isoflurane). No clinically significant concentrations of carbon monoxide are produced in the presence of normally hydrated absorbents. Care should be taken to follow manufacturer's instructions for CO_2 absorbents.

Isoflurane has been reported to interact with dry carbon dioxide absorbents during closed circuit anaesthesia, to form carbon monoxide. In order to minimize the risk of formation of carbon monoxide in rebreathing circuits and the possibility of elevated carboxyhaemoglobin levels, carbon dioxide adsorbents should not be allowed to dry out.

Rare cases of extreme heat, smoke and/or spontaneous fire in the anaesthesia machine have been reported during the administration of general anaesthesia with drugs in this class when used in conjunction with desiccated CO_2 absorbents, specifically those containing potassium hydroxide (e.g. Baralyme).
When a clinician suspects that the CO_2 absorbent may be desiccated, it should be replaced before administration of isoflurane. The colour indicator of most CO_2 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_2 absorbents should be replaced routinely regardless of the state of the colour indicator.

General

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 or techniques during which inspired or expired concentrations can be monitored, should be used. The degree of hypotension and respiratory
depression may provide some indication of anaesthetic depth.

As with any potent general anaesthetic, isoflurane should only be administered in an adequately equipped anaesthetising environment by those who are familiar with the pharmacology of the drug and qualified by training and experience to manage the anaesthetised patient.

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 anaesthetics, especially if the interval is less than 3 months, may increase the potential for hepatic injury. Cirrhosis, viral hepatitis or other pre-existing liver disease can be a reason to select an anaesthetic other than a halogenated
anaesthetic.

Regardless of the anaesthetics employed, maintenance of normal haemodynamics is important to the avoidance of myocardial ischaemia in patients with coronary artery disease.

Isoflurane markedly increases cerebral blood flow at deeper levels of anaesthesia. There may be a transient rise in cerebral spinal fluid pressure which is fully reversible with hyperventilation.

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

Use of isoflurane in hypovolaemic, hypotensive and debilitated patients has not been extensively investigated. A lower concentration of isoflurane is recommended for use in these patients.

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

Isoflurane may cause a slight decrease in intellectual function for 2-4 days following anaesthesia. Small changes in moods and symptoms may persist for up to 6 days after administration. This must be taken into account when patients resume normal daily activities, including driving or operating heavy machinery (please refer to section 4.7).

A potentiation of neuromuscular fatigue can be seen in patients with neuromuscular diseases, such as myasthenia gravis. Isoflurane should be used with caution in these patients.

Isoflurane should be administered with caution to patients who can develop bronchoconstriction since bronchospasm can occur (see section 4.8).

Isoflurane may cause respiratory depression which may be augmented by narcotic premedication or other agents causing respiratory depression.
Respiration should be supervised and if necessary, assisted (see section 4.8).

During the induction of anaesthesia, saliva flow and tracheobronchial secretion can increase and can be the cause of laryngospasm, particularly in children (see section 4.8).

Paediatric Population

Children under two years of age

Caution should be exercised when Isoflurane is used in small children due to limited experience with this patient group.

During the induction of anaesthesia, saliva flow and tracheobronchial secretion can increase and can be the cause of laryngospasm, particularly in children.

Malignant Hyperthermia

In susceptible individuals, isoflurane anaesthesia 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, tachypnoea, cyanosis, arrhythmias, and unstable blood pressures. (It should also be noted that many of these nonspecific signs may appear with light anaesthesia, acute hypoxia, etc.) An increase in overall metabolism may be reflected in an elevated temperature (which may rise rapidly early or late in the case, but usually is not the first sign of augmented metabolism) and an increased usage of the CO_2 absorption system (hot canister). PaO2 and pH may decrease, and hyperkalaemia and a base deficit may appear. Treatment includes discontinuance of triggering agents (e.g. isoflurane), intravenous administration of dantrolene sodium, and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support as indicated, and management of electrolyte-fluid-acidbase
derangements. (Consult prescribing information for dantrolene sodium intravenous for additional information on patient management.) Renal failure may appear later.

There have been postmarketing reports of malignant hyperthermia. Some of these reports have been fatal.

Perioperative hyperkalaemia

Use of inhaled anaesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in paediatric age

group 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, these patients did NOT have classical signs or symptoms of malignant hyperthermia such as muscle rigidity or hypermetabolic state. Prompt and vigorous treatment for hyperkalaemia and resistant arrhythmias is recommended as is subsequent evaluation for latent neuromuscular disease.

4.5 Interaction with other medicinal products and other forms of interaction

Combinations advised against:

Beta-sympathomimetic agents like isoprenaline, and alpha and beta-sympathomimetic agents like adrenaline and noradrenaline should be used with caution during isoflurane narcosis, due to a potential risk of ventricular arrhythmia.

Non-selective MAO-inhibitors: Risk of crisis during the operation. Treatment should be stopped 15 days prior to surgery.

Combinations requiring precautions in using:

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

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

Calcium antagonists, in particular dihydropyridine derivatives:

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

Caution should be exercised when calcium antagonists are used concomitantly with inhalation anaesthetics due to risk of additive negative inotropic effect.

Beta-blockers: Cardiovascular compensation reactions may be impaired by beta- blockers.

Inducers of CYP2E1

Medicinal products and compounds 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.

Use of Isoflurane and Isoniazid can increase the risk of potentiation of the hepatotoxic effects.

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

Concomitant use of succinylcholine with inhaled anaesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in paediatric patients during the post-operative period.

All commonly used muscle relaxants are markedly potentiated by Isoflurane. Neostigmine has an effect on the non-depolarising relaxants, but has no effect on the relaxing action of Isoflurane itself.
MAC (minimum alveolar concentration) is reduced by concomitant administration of N_2O in adults (see section 4.2).

4.6 Fertility, pregnancy and lactation

Pregnancy There are no or limited amount of data from the use of isoflurane in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).
Isoflurane should only be used during pregnancy if the benefit outweighs the potential risk.
Isoflurane, like other inhalational agents, has relaxant effects on the uterus with the potential risk for uterine bleeding. Clinical judgement should be observed when using isoflurane during obstetric anaesthesia. Consideration should be taken to use the lowest possible concentration of isoflurane in obstetrical operations.

Use in Caesarean Section
Isoflurane, in concentrations up to 0.75%, has been shown to be safe for the maintenance of anaesthesia for caesarean section (please refer to section 4.4).

Breastfeeding
It is not known whether isoflurane/metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when isoflurane is administered to a nursing woman.

4.7 Effects on ability to drive and use machines

Patients should be advised that performance of activities requiring mental alertness, such as operating a motor vehicle or hazardous machinery, may be impaired for 2-4 days after anaesthesia with isoflurane. As with other anaesthetics, small changes in moods and symptoms may persist for up to 6 days after administration (see Section 4.4).

4.8 Undesirable effects

a. Summary of the safety profile

Adverse reactions encountered in the administration of Isoflurane are in general dose dependent extensions of pharmaco-physiological effects and include hypotension, respiratory depression and arrhythmias. Potential serious undesirable effects include malignant hyperthermia, hyperkalaemia, elevated serum creatine kinase, myoglobinuria, anaphylactic reactions and liver adverse reactions (please refer to section 4.4 and 4.8). Shivering, nausea, vomiting, ileus, agitation and delirium have been observed in the post-operative period.

Cardiac arrest, bradycardia and tachycardia have been observed with general inhalation anaesthetic drugs including isoflurane.
Reports of QT prolongation, associated with torsade de pointes (in exceptional cases, fatal) have been received.

b. Tabulated summary of adverse reactions

The following table displays adverse reactions reported in clinical trials and from post-marketing experience. Frequency cannot be estimated from the available data, therefore it is "not known".

SUMMARY OF MOST FREQUENT ADVERSE DRUG REACTIONS		
SOC	**FREQUENCY**	**ADVERSE REACTIONS**
Blood and lymphatic system disorders	Not known	Carboxyhaemoglobinaemia[2]
Immune system disorders	Not known	Anaphylactic reaction[1]
	Not known	Hypersensitivity[1]
Metabolism and nutrition disorders	Not known	Hyperkalaemia[2]
	Not known	Blood glucose increased[1]
Psychiatric disorders	Not known	Agitation
	Not known	Delirium
	Not known	Mood altered[5]
Nervous system disorders	Not known	Convulsion
	Not known	Mental impairment[4]
Cardiac disorders	Not known	Arrhythmia
Vascular disorders	Not known	Hypotension[2]
	Not known	Haemorrhage[3]
Respiratory, thoracic and mediastinal disorders	Not known	Bronchospasm[2]
	Not known	Dyspnoea[1]
	Not known	Wheezing[1]

	Not known	Respiratory depression[2]
	Not known	Laryngospasm[2]
Gastrointestinal disorders	Not known	Ileus
	Not known	Vomiting
	Not known	Nausea
Hepatobiliary disorders	Not known	Hepatic necrosis[2]
	Not known	Hepatocellular injury[2]
	Not known	Blood bilirubin increased[1]
Skin and subcutaneous tissue disorders	Not known	Swelling face[1]
	Not known	Dermatitis contact[1]
	Not known	Rash[1]
Renal and urinary disorders	Not known	Blood creatinine increased[1]
	Not known	Blood urea decreased[1]
General disorders and administration site conditions	Not known	Hyperthermia malignant[2]
	Not known	Chest discomfort[1]
	Not known	Chills
Investigations	Not known	White blood cell count increased[1]
	Not known	Hepatic enzyme increased[2]
	Not known	Fluoride increased[1]
	Not known	Electroencephalogram abnormal
	Not known	Blood cholesterol decreased[1]
	Not known	Blood alkaline phosphatase decreased[1]

[1]See 4.8(c).
[2]See 4.4.
[3]In patients undergoing induced abortion. See 4.4.
[4]May cause a slight decrease in intellectual function for 2-4 days after anaesthesia. See 4.4.
[5]Small changes in moods and symptoms may persist for up to 6 days. See 4.4.

c. Description of selected adverse reactions

Transient increases in blood bilirubin, blood glucose and serum creatinine with decrease in BUN, serum cholesterol and alkaline phosphatase have been observed. As with other general anaesthetics, transient elevations in white blood count have been observed even in the absence of surgical stress.

Rare reports of hypersensitivity (including dermatitis contact, rash, dyspnoea, wheezing, chest discomfort, swelling face, or anaphylactic reaction) have been received, especially in association with long-term occupational exposure to inhaled anaesthetic agents, including isoflurane. These reactions have been confirmed by clinical testing (e.g., methacholine challenge). The etiology of anaphylactic reactions experienced during inhalational anaesthetic exposure is, however, unclear because of the exposure to multiple concomitant drugs, many of which are known to cause such reactions. Minimally raised levels of serum inorganic fluoride occur during and after isoflurane anaesthesia, due to biodegradation of the agent. It is unlikely that the low levels of serum inorganic fluoride observed (mean 4.4 μmol/l in one study) could cause renal toxicity, as these are well below the proposed threshold levels for kidney toxicity.

d. Paediatric population
Use of inhaled anaesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in paediatric patients during the post-operative period. (See 4.4.)

During the induction of anaesthesia, saliva flow and tracheobronchial secretion can increase and can be the cause of laryngospasm. (See 4.4.)

e. Other special populations
Neuromuscular disease:
Use of inhaled anaesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in paediatric patients during the post-operative period. Patients with latent as well as overt neuromuscular disease, particularly Duchenne muscular dystrophy, appear to be most vulnerable. Early and aggressive intervention to treat the hyperkalaemia and resistant arrhythmias is recommended, as is subsequent evaluation for latent neuromuscular disease (see section 4.4).

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

As with other halogenated anaesthetics, hypotension and respiratory depression have been observed. Close monitoring of blood pressure and respiration is recommended. Supportive measures may be necessary to correct hypotension and respiratory depression resulting from excessively deep levels of anaesthesia.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nervous system; anaesthetic; general; Halogenated hydrocarbons; ATC code: N01AB06.

Isoflurane is a general inhalational anaesthetic which provides rapid induction of anaesthesia and also rapid recovery. Although slight pungency may limit the rate of induction, excessive salivation and tracheo-bronchial secretions are not stimulated. Pharyngeal and laryngeal reflexes are diminished quickly. Levels of anaesthesia change rapidly with Isoflurane. Heart rhythm remains stable. Spontaneous respiration becomes depressed as depth of anaesthesia increases and should be closely monitored.

During induction there is a decrease in blood pressure which returns towards normal with surgical stimulation.

Blood pressure tends to fall during maintenance in direct relation to depth of anaesthesia, due to peripheral vasodilation, but cardiac rhythm remains stable. With controlled respiration and normal $PaCO_2$, cardiac output tends to be maintained despite increasing depth of anaesthesia, primarily through a rise in heart rate. With spontaneous respiration, the resulting hypercapnia may increase heart rate and cardiac output above awake levels.

Cerebral blood flow remains unchanged during light isoflurane anaesthesia but tends to rise at deeper levels. Increases in cerebrospinal fluid pressure may be prevented or reversed by hyperventilating the patient before or during anaesthesia. Electro- encephalographic changes and convulsion are extremely rare with isoflurane.

Isoflurane appears to sensitise the myocardium to adrenaline to an even lesser extent than Enflurane. Limited data suggest that subcutaneous infiltration of up to 50ml of 1:200,000 solution adrenaline does not induce ventricular arrhythmias, in patients anaesthetised with isoflurane.

Muscular relaxation may be adequate for some intra-abdominal operations at normal levels of anaesthesia, but should greater relaxation be required small doses of intravenous muscle relaxants may be used. All commonly used muscle relaxants are markedly potentiated by isoflurane, the effect being most profound with non- depolarising agents. Neostigmine reverses the effects of non-depolarising muscle relaxants but has no effect on the relaxant properties of isoflurane itself. All commonly used muscle relaxants are compatible with isoflurane.

Isoflurane may be used for the induction and maintenance of general

anaesthesia. Adequate data are not available to establish its place in pregnancy or obstetric anaesthesia other than for caesarean section.
Relatively little metabolism of isoflurane occurs in the human body. In the post operative period only 0.17% of the isoflurane taken up can be recovered as urinary metabolites. Peak serum inorganic fluoride values usually average less than 5µmol/litre and occur about four hours after anaesthesia, returning to normal levels within 24 hours. No signs of renal injury have been reported after isoflurane administration.

5.2 Pharmacokinetic properties

MAC (Minimum Alveolar Concentration in man)

Age	100% Oxygen	70%N_2O
26 ± 4	1.28	0.56
44 ± 7	1.15	0.50
64 ± 5	1.05	0.37

5.3 Preclinical safety data

Published studies in animals (including primates) at doses resulting in light to moderate anaesthesia demonstrate that the use of anaesthetic agents during the period of rapid brain growth or synaptogenesis results in cell loss in the developing brain that can be associated with prolonged cognitive deficiencies. The clinical significance of these nonclinical findings in not known.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

Isoflurane has been reported to interact with dry carbon dioxide absorbents to form carbon monoxide. In order to minimise the risk of formation of carbon monoxide in rebreathing circuits and the possibility of elevated carboxyhaemoglobin levels, carbon dioxide absorbents should not be allowed to dry out. (See also section 4.4).

6.3 Shelf life

5 years

6.4 Special precautions for storage

Do not store above 30°C. Keep the container tightly closed. Keep out of the sight and reach of children.

6.5 Nature and contents of container

Amber glass Type III nominal 100 ml or 250 ml bottle with black screw cap and polyethylene cone.

6.6 Special precautions for disposal

Vaporisers specially calibrated for isoflurane should be used so that the concentration of anaesthetic delivered can be accurately controlled.

It is recommended that vapour from this and other inhalation agents be efficiently extracted from the area of use.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 37071/0002

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10 DATE OF REVISION OF THE TEXT

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