

Summary of Product Characteristics (SmPC)

1. Name of the medicinal product

Isoflurane-AIT

2. Qualitative and quantitative composition

Each 1 ml contains:

Isoflurane NLT 99.9% w/w

3. PHARMACEUTICAL FORM

Isoflurane- AIT Is Liquid For Inhalation with Clear Colorless Mobile Heavy non-flammable Liquid With a Characteristic Odour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Isoflurane- AIT is indicated as a general anaesthetic by inhalation.

4.2 Posology and method of administration

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

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
<u>26 ± 4 years</u>	<u>1.28%</u>	<u>0.56%</u>
<u>44 ± 7 years</u>	<u>1.15%</u>	<u>0.50%</u>
<u>64 ± 5 years</u>	<u>1.05%</u>	<u>0.37%</u>

PAEDIATRIC POPULATION	
Age	Average MAC Value in 100% Oxygen
<u>Preterm neonates</u> <u>< 32 weeks gestational age</u>	<u>1.28%</u>
<u>Preterm neonates</u>	<u>1.41%</u>

<u>32-37 weeks gestational age</u>	
<u>0-1 month</u>	<u>1.60%</u>
<u>1-6 months</u>	<u>1.87%</u>
<u>6-12 months</u>	<u>1.80%</u>
<u>1-5 years</u>	<u>1.60%</u>

Premedication: Drugs used for premedication should be selected for the individual patient bearing in mind the respiratory depressant effect of isoflurane-AIT. The use of anticholinergic drugs is a matter of choice, but may be advisable for inhalation induction in paediatrics.

Induction of anaesthesia in adults: A short-acting barbiturate or other intravenous induction agent is usually administered followed by inhalation of the isoflurane-AIT mixture.

Alternatively, isoflurane-AIT with oxygen or with an oxygen/nitrous oxide mixture may be used.

It is recommended that induction with isoflurane-AIT be initiated at a concentration of 0.5%.

Concentrations of 1.5 to 3.0% usually produce surgical anaesthesia in 7 to 10 minutes.

Induction of anaesthesia in children: Isoflurane-AIT 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: Surgical levels of anaesthesia may be maintained with 1.0-2.5% isoflurane-AIT in oxygen/nitrous oxide mixtures. An additional 0.5-1.0% isoflurane-AIT may be required when given with oxygen alone.

For caesarean section, 0.5-0.75% isoflurane-AIT 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-AIT concentrations in the absence of other complicating factors.

Excessive falls in blood pressure may be due to depth of anaesthesia and in these circumstances, should be corrected by reducing the inspired isoflurane-AIT concentration.

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

4.3 Contraindications

Isoflurane-AIT is contra-indicated in patients with known sensitivity to Isoflurane-AIT or other halogenated anaesthetics. It is also contra-indicated in patients with known or suspected genetic susceptibility to malignant hyperpyrexia.

4.4 Special warnings and precautions for use

Vaporisers specially calibrated for isoflurane-AIT 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-AIT to patients at risk for QT prolongation.

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

Isoflurane-AIT, 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-AIT during obstetric anaesthesia. Consideration should be taken to use the lowest possible concentration of isoflurane-AIT in obstetrical operations (please refer to section 4.6).

Isolated cases of increased carboxyhaemoglobin have been reported with the use of fluorinated inhalation agents (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 CO₂absorbents.

Isoflurane-AIT 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 absorbent 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 CO₂ absorbents, specifically those containing potassium hydroxide (e.g. Baralyme). When a clinician suspects that the CO₂absorbent may be desiccated, it should be replaced before administration of isoflurane-AIT. The colour indicator of most CO₂

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. CO₂ absorbents should be replaced routinely regardless of the state of the colour indicator.

General

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.

Since levels of anaesthesia may be altered quickly and easily with isoflurane, only vaporisers which deliver a predictable output with reasonable accuracy, or techniques during which inspired or expired concentrations can be monitored, should be used. The degree of hypotension and respiratory depression may provide some indication of anaesthetic depth.

Reports demonstrate that isoflurane can produce hepatic injury ranging from mild transient increases of liver enzymes to fatal hepatic necrosis in very rare instances. It has been reported that previous exposure to halogenated hydrocarbon anaesthetics, especially if the interval is less than 3 months, may increase the potential for hepatic injury. Cirrhosis, viral hepatitis or other preexisting liver disease can be a reason to select an 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-AIT in hypovolaemic, hypotensive and debilitated patients has not been extensively investigated. A lower concentration of isoflurane-AIT is recommended for use in these patients.

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

Isoflurane-AIT 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-AIT should be used with caution in these patients.

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

Isoflurane-AIT 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).

Children Under Two Years of Age

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

Malignant Hyperthermia

In susceptible individuals, isoflurane-AIT 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.). PaO_2 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-acid-base derangements. (Consult prescribing information for dantrolene sodium intravenous for additional information on patient management.) Renal failure may appear later.

There have been post marketing 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 patients during the post-operative 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 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 betasympathomimetic agents like adrenaline and noradrenaline should be used with caution during isoflurane-AIT 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-AIT than in the case of halothane.

Cardiovascular compensation reactions may be impaired by beta-blockers.

Medicinal products and compounds that increase the activity of cytochrome P450 isoenzyme CYP2E1, such as isoniazid and alcohol, may increase the metabolism of isoflurane-AIT and lead to significant increases in plasma fluoride concentrations.

Use of isoflurane-AIT and isoniazid can increase the risk of potentiation of the hepatotoxic effects.

Calcium antagonists, in particular dihydropyridine derivatives: isoflurane-AIT may lead to marked hypotension in patients treated with calcium antagonists.

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

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

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, the effect being most profound with non-depolarizing agents. 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 N₂O in adults (see section 4.2).

4.6 Fertility, pregnancy and lactation

Use in Pregnancy

There are no or limited amount of data from the use of isoflurane-AIT in pregnant women.

Isoflurane-AIT should only be used during pregnancy if the benefit outweighs the potential risk (please refer to section 4.4).

Use in Caesarean Section

Isoflurane-AIT, 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).

Nursing Mothers

It is not known whether isoflurane-AIT/metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when isoflurane-AIT 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-AIT. 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-AIT are in general dose dependent extensions of pharmaco-physiologic effects and include respiratory depression, hypotension 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-AIT.

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 Not known Not known	Agitation Delirium Mood altered ⁵
Nervous system disorders	Not known Not known	Convulsion Mental impairment ⁴
Cardiac disorders	Not known Not known Not known Not known Not known	Arrhythmia Bradycardia Cardiac arrest Electrocardiogram QT prolonged Tachycardia Torsade de pointes
Vascular disorders	Not known Not known	Hypotension ² Haemorrhage ³
Respiratory, thoracic and mediastinal disorders	Not known Not known Not known Not known Not known	Bronchospasm ² Dyspnoea ¹ Wheezing ¹ Respiratory depression ² Laryngospasm ²
Gastrointestinal disorders	Not known Not known Not known	Ileus Vomiting Nausea
Hepatobiliary disorders	Not known Not known Not known	Hepatic necrosis ² Hepatocellular injury ² Blood bilirubin increased ¹
Skin and subcutaneous tissue disorders	Not known Not known Not known	Swelling face ¹ Dermatitis contact ¹ Rash ¹
Renal and urinary disorders	Not known Not known	Blood creatinine increased ¹ Blood urea decreased ¹

General disorders and administration site conditions	Not known	Malignant hyperthermia 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
Musculoskeletal and connective tissue disorders	Not known	Myoglobinuria
	Not known	Rhabdomyolysis

¹See 4.8(c).

²See 4.4.

³In patients undergoing induced abortion. See 4.4.

⁴May cause a slight decrease in intellectual function for 2-4 days after anaesthesia. See 4.4.

⁵Small 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-AIT. 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-AIT 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 section 4.4.) During the induction of anaesthesia, saliva flow and tracheobronchial secretion can increase and can be the cause of laryngospasm. (See section 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).

Older people:

Lesser concentrations of isoflurane-AIT are normally required to maintain surgical anaesthesia in elderly patients. (See section 4.2.)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 Egypt-
pv.followup@edaegypt.gov.eg

Email: qppv@acdimatrading.com

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.

5.1 Pharmacodynamic properties

Induction and particularly recovery are rapid. 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.

Paediatric

Some published studies in children have observed cognitive deficits after repeated or prolonged exposures to anaesthetic agents early in life. These studies have substantial limitations, and it is not clear if the observed effects are due to the anaesthetic/sedation drug administration or other factors such as the surgery or underlying illness. In addition, more recent published registry studies did not confirm these findings.

5.2 Pharmacokinetic properties

MAC (Minimum Alveolar Concentration in man):

Age 100% Oxygen 70% N₂O

26 ± 4

44 ± 7

64 ± 5 1.28

1.15

1.05 0.56

0.50

0.37

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).

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

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at temperature not exceeding 30°C protected from light.

6.5 Nature and contents of container

Carton box contains amber (type III) glass bottle with polypropylene cap containing 100ml liquid for inhalation and insert leaflet.

Manufactured by:

ACDIMA INTERNATIONAL TRADING

Plot 41 Industriaila Zone Extension,

6th October City, Egypt.