Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Evorane 99.9% w/w, Inhalation Vapor, Liquid

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Isoflurane (not less than 99.9% w/w).

3 PHARMACEUTICAL FORM

Inhalation Vapor, Liquid.

Clear colorless liquid with slightly musty odor for vaporization and administration as an inhalation gas.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Induction and maintenance of general anesthesia in adults and children. Use of isoflurane in dental anesthesia should be restricted to hospitals or day care units only (see section 4.3).

4.2 Posology and method of administration

Posology

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

Overall, MAC values for Evorane diminish with age. The table below indicates average MAC values for different age groups.

ADULTS	**Age**	**Average MAC Value in 100 % Oxygen**	**70% N_2O**
	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%

Method of administration

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

Induction:
To avoid excitement an intravenous induction agent should be administered followed by inhalation of Evorane. Evorane with oxygen or with an oxygen/nitrous oxide mixture may be used.

It is recommended that induction with Evorane be initiated at a concentration of 0.5%. Concentrations of 1.5 to 3.0%
usually produce surgical anesthesia in 7 to 10 minutes.

Induction of anesthesia 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:
Surgical levels of anesthesia may be maintained with 1.0 - 2.5% Evorane in oxygen/nitrous oxide mixtures. An additional 0.5-1.0% Evorane may be required when given with oxygen alone. For caesarian section, 0.5-0.75% Evorane in a mixture of oxygen/nitrous oxide is suitable.

Arterial pressure levels during maintenance tend to be inversely related to alveolar Evorane concentrations in the absence of other complicating factors. Excessive falls in blood pressure (unless due to hypovolemia) may be related to depth of anesthesia and, in these circumstances, should be corrected by reducing the inspired Evorane concentration.

Older patients:
As with other agents, lesser concentrations of Evorane are normally required to maintain surgical anesthesia in elderly patients. See above for MAC values.

4.3 Contraindications

Use in patients in whom liver dysfunction, jaundice or unexplained fever, leukocytosis or eosinophilia has occurred after a previous halogenated anesthetic administration.

Evorane is contra-indicated in patients with known sensitivity to Evorane or other halogenated anesthetics. It is also contraindicated in patients with known or suspected genetic susceptibility to malignant hyperthermia.

Evorane is contraindicated in all patients (adults and children) undergoing dental procedures outside a hospital or day care unit (see section 4.4).

4.4 Special warnings and precautions for use

Vaporizers specially calibrated for Evorane should be used so that the concentration of anesthetic delivered can be accurately controlled. Hypotension and respiratory depression increase as anesthesia is deepened.

Increased blood losses comparable with those found following anesthesia with other inhalation agents have been recorded with isoflurane in patients undergoing uterine curettage.

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

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. (see section 4.8).

Caution should be exercised in administering general anesthesia, including isoflurane, to patients with mitochondrial

disorders.

General

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

Since levels of anesthesia may be altered quickly and easily with Evorane, only vaporizers 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 anesthetic depth.

Reports demonstrate that isoflurane can produce hepatic injury ranging from mild transient increases in 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. Cirrhosis, viral hepatitis or other preexisting liver disease can be a reason to select an anesthetic other than a halogenated anesthetic. All patients anaesthetized with Evorane should be constantly monitored, including ECG, BP, oxygen saturation and end tidal CO_2 in a setting where full resuscitative equipment is available and with staff fully trained in resuscitative techniques. The presence of additional risk factors should be taken into consideration (see section 4.8).

Hypotension and myocardial depression are related to the depth of anesthesia. The concomitant use of nitrous oxide and surgical stimulation may limit the extent of the hypotension. Excessive fall in blood pressure, unless due to hypovolemia, should be corrected by lightening the depth of anesthesia.

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

Isoflurane markedly increases cerebral blood flow at deeper levels of anesthesia. There may be a transient rise in cerebral spinal fluid pressure which is reversible with hyperventilation.
Isoflurane must be used with caution in patients with increased intracranial pressure. In such cases hyperventilation may be necessary. This should be borne in mind when considering use in neurosurgery.

Use of isoflurane in hypovolemic, 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- depolarizing agents.

Isoflurane may cause a slight decrease in intellectual function for 2-4 days following anesthesia. 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 (see to section 4.7).

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

Evorane 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). Measurement of tidal volume may provide an indication of depth of anesthesia in the spontaneously breathing patient.

During the induction of anesthesia, 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 Evorane is used in small children due to limited experience with this patient-group.

Malignant hyperthermia: In susceptible individuals, Evorane (isoflurane) anesthesia may trigger a skeletal muscle hyper metabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. The syndrome includes non-specific features such as muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and unstable blood pressures. (It should also be noted that many of these non-specific signs may appear with light anesthesia, acute hypoxia, etc.) PaO_2 and pH may decrease and hyperkalemia and a base deficit may appear.

There have been post marketing reports of malignant hyperthermia. Some of these reports have been fatal.

Treatment includes discontinuance of triggering agents (e.g. Evorane). 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 and urine flow should be sustained if possible.

Perioperative Hyperkalemia
Use of inhaled anesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in pediatric patients 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 of hyper metabolic state. Early and aggressive intervention to treat the hyperkaliemia and resistant
arrhythmias is recommended, as is subsequent evaluation for latent neuromuscular disease.

Although peak inorganic fluoride concentrations which result from the breakdown of isoflurane are generally much lower than those considered 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.

This agent should be administered cautiously to those on anti hypertensive or any drug which may influence the response of the sympathetic nervous system.

Isolated cases of increased carboxyhemoglobin 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 manufacturers' instructions for CO_2 absorbents.

Standard anesthesia monitors such as pulse oximeters are not a reliable method for detecting

carboxyhaemoglobin. Direct measurement of carboxyhaemoglobin should be carried out in the event that a

patient on closed circuit
anesthesia with an implicated agent develops oxygen desaturation which does not respond to the usual therapeutic measures.

Rare cases of extreme heat, smoke and/or spontaneous fire in the anesthesia machine have been reported during the administration of general anesthesia 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 color indicator of most CO_2 absorbents does not necessarily change as a result of desiccation.
Therefore, the lack of significant color change should not be taken as an assurance of adequate hydration. CO_2 absorbents should be replaced routinely regardless of the state of the color indicator.

4.6 Interaction with other medicinal products and other forms of interaction

Combinations advised against:

Concomitant use of succinylcholine with inhaled anesthetic 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.

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:

Inducers of CYP2EI: 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.

Indirect-acting sympathomimetics (amphetamines and their derivatives, psychostimulants, appetite suppressants, ephedrine and its derivatives): Risk of perioperative 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.

Cardiovascular compensation reactions may be impaired by beta-blockers.

Calcium antagonists, in particular dihydropyridine derivates: 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 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.

All commonly used muscle relaxants are markedly potentiated by isoflurane, the effect being most profound with non- depolarising agents. Neostigmine has an effect on the nondepolarising relaxants, but has no effect on the relaxing action of isoflurane itself. Care should also be exercised when using antibiotics of the aminoglycoside group e.g. neomycin, concurrently with isoflurane.

Isoflurane does not sensitise the myocardium to the effects of catecholamines in dogs. Limited data suggests that subcutaneous infiltration of 0.25 mg (50 ml of 1:200,000 solution) adrenaline of 3.4 mcg/kg in a 70 kg adult, does not produce an increase in ventricular arrhythmias, provided there is no concomitant myocardial hypoxia. The utmost care must be used to prevent overdosage or unduly rapid adrenaline absorption.

MAC (minimum alveolar concentration) is reduced by concomitant administration of N20 in adults (see section 4.2).

4.7 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. 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 judgment should be exercised when using isoflurane during obstetric anaesthesia. Consideration should be taken to use the lowest possible concentration of isoflurane in obstetrical operations.

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

Breast-feeding
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.

4.8 Effects on ability to drive and use machines

Isoflurane can have an influence on driving and using machines. The patient should not drive or use machines for 2-4 days following anaesthesia with isoflurane. Changes in behaviour and intellectual function 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.

4.9 Undesirable effects

a. Summary of the safety profile
Adverse reactions encountered in the administration of isoflurane are in general dose dependent extensions of pharmacophysiologic effects and include respiratory depression, hypotension and arrhythmias. Potential serious undesirable effects include malignant hyperthermia, anaphylactic reactions,liver adverse reactions, hyperkalemia,
elevated serum creatine kinase and myoglobinuria (see sections 4.4 and 4.8). Shivering, nausea, vomiting, ileus, agitation and delirium have been observed in the postoperative period.

Cardiac arrest, bradycardia, and tachycardia have been observed with general inhalation anaesthetic drugs including isoflurane.

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 "unknown".

Summary of Most Frequent Adverse Drug Reactions

SOC	Frequency	Adverse Reactions
Blood and lymphatic system disorders	Unknown	Carboxyhaemoglobinaemia[2]
Immune system disorders	Unknown	Anaphylactic reaction[1]
	Unknown	Hypersensitivity[1]
Metabolsim and nutrition disorders	Unknown	Hyperkalaemia[2]
	Unknown	Blood glucose increased[1]
Psychiatric disorders	Unknown	Agitation
	Unknown	Delirium
	Unknown	Mood altered[5]
Nervous system disorders	Unknown	Convulsion
	Unknown	Mental impairment[4]

Cardiac disorders	Unknown	Arrhythmia
	Unknown	Cardiac arrest
	Unknown	Bradycardia
	Unknown	Tachycardia
	Unknown	Electrocardiogram QT prolonged[1]
	Unknown	Torsade de pointes[1]
Vascular disorders	Unknown	Hypotension[2]
Respiratory, thoracic and mediastinal disorders	Unknown	Haemorrhage[3]
	Unknown	Bronchospasm[1,2]
	Unknown	Dyspnoea[1]
	Unknown	Wheezing[1]
	Unknown	Respiratory depression[2]
	Unknown	Laryngospasm[1,2]
Gastrointestinal disorders	Unknown	Ileus
	Unknown	Vomiting
	Unknown	Nausea
Hepatobiliary disorders	Unknown	Hepatic necrosis[2]
	Unknown	Hepatocellular injury[2]
	Unknown	Blood bilirubin increased.[1]
Skin and subcutaneous tissue disorders	Unknown	Swelling face[1]
	Unknown	Dermatitis contact[1]
	Unknown	Rash[1]
Renal and urinary disorders	Unknown	Blood creatinine increased[1]
	Unknown	Blood urea decreased
General disorders and administration site conditions	Unknown	Hyperthermia malignant[2]
	Unknown	Chest discomfort[1]
	Unknown	Chills
Investigations		White blood cell
Unknown		count increased[1]
	Unknown	Hepatic enzyme increased[2]
	Unknown	Fluoride increased[1]
	Unknown	Electroencephalogram abnormal
	Unknown	Blood cholesterol decreased[1]
	Unknown	Blood alkaline phosphatase decreased[1]
Musculoskeletal and connective tissue disorders	Unknown	Myoglobinuria
	Unknown	Rhabdomyolysis

[1]See 4.8(c)

[2]See 4.4

[3] Isoflurane, like other inhalational agents, has relaxant effects on the uterus with the potential risk for uterine bleeding. See 4.4.

[4]May cause a slight decrease in intellectual function for 2-4 days after anesthesia. 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 all other general anesthetics, 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 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.

Minimally raised levels of serum inorganic fluoride occur during and after isoflurane anesthesia, due to biodegradation of the agent. It is unlikely that the low levels of serum inorganic fluoride observed (mean 4.4 μ mol/l in one study) could cause renal toxicity, as these are well below the proposed threshold levels for kidney toxicity.

Bronchospasm and laryngospasm due to airway irritation have been reported with volatile anesthetics during inhalation.

Reports of QT prolongation, associated with torsade de pointes (in exceptional cases, fatal), have been received.

d. Pediatric population

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. (see section 4.4.)

During the induction of anesthesia, 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 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 Duchene muscular dystrophy, appear to be most vulnerable. Early and
aggressive intervention to treat the hyperkaliemia 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 anesthesia in elderly patients. (see section 4.2.)

4.10 Overdose

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 anesthesia.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

ATC Code: N01AB06 Halogenated hydrocarbon.
Induction and particularly recovery are rapid. Although slight pungency may limit the rate of induction, excessive salivation and tracheobronchial secretions do not appear to be stimulated. Pharyngeal and laryngeal reflexes are diminished quickly. Levels of anesthesia change rapidly with Evorane. Heart rhythm remains stable.

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

Evorane appears to sensitize the myocardium to adrenaline. Limited data suggest that subcutaneous infiltration of up to 50 ml of 1:200,000 solution adrenaline does not induce ventricular arrhythmias in patients anaesthetized with Evorane (See also Section 4.5).

Muscular relaxation may be adequate for some intra-abdominal operations at normal levels of anesthesia, but should greater relaxation be required small doses of intravenous muscle relaxants may be used. All commonly used muscle relaxants are markedly potentiated by Evorane, the effect being most profound with non-depolarizing agents. Neostigmine reverses the effects of non-depolarizing muscle relaxants but has no effect on the relaxant properties of Evorane itself. All commonly used muscle relaxants are compatible with Evorane (see also Section 4.5).

5.2 Pharmacokinetic properties

Evorane undergoes minimal biotransformation in man. In the post-operative period only 0.17% of the Evorane taken up can be recovered as urinary metabolites. Peak serum inorganic fluoride values usually average less than 5 µmol/liter and occur about four hours after anesthesia, returning to normal levels within 24 hours. No signs of renal injury have been reported after Evorane administration.

5.3 Preclinical safety data

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

Some halogenated inhalation agents with a CH-F_2 moiety, i.e. desflurane, isoflurane and enflurane have been reported to interact with dry CO_2 absorbents to form carbon monoxide. In order to minimize the risk of formation of carbon monoxide in closed and re-breathing circuits, and the possibility of increased carboxyhaemoglobin levels in exposed patients, CO_2 absorbents should not be allowed to dry out (see also section 4.4).

6.3 Shelf life

3 years.
In-use stability: Use within 3 months from opening when stored in the original package and below 25^{o}C.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package in order to protect from light. Keep the bottle tightly closed.

6.5 Nature and contents of container
100-mL and 250ml amber soda-lime glass bottle, closed with an aluminum cap with LDPE liner.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Vaporizers specially calibrated for Evorane should be used so that the concentration of anesthetic delivered can be accurately controlled.

It is recommended that vapor 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 NAME AND ADDRESS OF MANUFACTURER

MAH: AMB HK ENTERPRISES (PVT) LTD.
7.1 Hebei YiPin Pharmaceutical Co., Ltd.
Sanxia road, Economy Technology Area of Shijiazhuang, Hebei, China

8 PRODUCT REGISTRATION NUMBER

115712

9 DATE OF REGISTRATION

18-10-2023