PHYSICIAN'S PRESCRIBING INFORMATION

1. NAME OF THE MEDICINAL PRODUCT

Isoflurane USP, Terrell™

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Isoflurane 100%

Each 100 ml bottle Isoflurane contains 100 ml isoflurane.

Each 250 ml bottle Isoflurane contains 250 ml isoflurane.

3. PHARMACEUTICAL FORM

Liquid for inhalation

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For general inhalation anaesthesia.

4.2 Posology and method of administration

In order to be able to accurately control the precise concentration of isoflurane, vaporisers that have been specially calibrated for isoflurane should be used.

Induction of anaesthesia:

If isoflurane is used for induction of anaesthesia, a starting concentration of 0.5% is recommended. Concentrations of 1.3-3.0% usually bring about surgical anaesthesia within 7 to 10 minutes.

It is recommended that use be made of a hypnotic dose of a short acting barbiturate oranother product such as propofol, etomidate, or midazolam in order to avoid coughing or laryngospasm, which can arise if induction is carried out with Isoflurane alone or in combination with oxygen or with an oxygen-nitrous oxide mixture.

Maintenance of anaesthesia:

Anaesthesia can be maintained during surgery using a concentration of 1.0-2.5% with the simultaneous administration of N_2O and O_2.

A higher concentration of 1.5-3.5% of Isoflurane is necessary if Isoflurane is administered with pure oxygen.

Recovery:

The concentration of Isoflurane must be reduced to 0.5% at the end of the operation, orto 0% during closure of the wound to allow prompt recovery.

If all administration of anaesthetic agents has been stopped, the air passages of thepatient should be ventilated several times with 100% oxygen until complete awakening occurs.

If the vector gas is a mixture of 50% O_2 and 50% N_2O, the value of the minimum alveolar concentration of isoflurane is approximately 0.65%.

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

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

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).

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.

4.3 Contraindications

- Isoflurane is contraindicated in patients with known sensitivity to isoflurane or 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

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

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

Hypotension and respiratory depression increase as anesthesia is deepened.

Since levels of anesthesia may be altered quickly and easily with isoflurane, 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 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 anesthesia, including isoflurane, to patients with mitochondrial disorders.

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

It has been reported that previous exposure to halogenated hydrocarbon anesthetics, especially if the interval is less than 3 months, may increase the potential for hepatic injury.

Cirrhosis, viral hepatitis, or other pre-existing liver disease can be a reason to select an anaesthetic other than a halogenated anaesthetic.

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).
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 5 micromol/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.

There is insufficient experience of use in repeated anaesthesia to make a definitive recommendation in this regard. As with all halogenated anaesthetics repeat anaesthesia within a short period of time should be approached with caution.

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 markedly increases cerebral blood flow at deeper levels of anesthesia. 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. Isoflurane should be administered with caution to patients who can develop bronchoconstriction since bronchospasms can occur (see section 4.8).

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.

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

In light of the fact that Isoflurane acts in an irritating manner on the mucous membranes, the product is difficult to use if inhalation anaesthesia is applied via mask. During the induction of anaesthesia, saliva flow and tracheobronchial secretion can increase and can be the cause of laryngospasms, particularly in children (see section 4.8).

Increased blood losses comparable with those found following anaesthesia with other inhalation agents have been recorded with isoflurane in patients undergoing induced abortion.

Isoflurane relaxes the uterus muscle, and the lowest possible concentration of isoflurane should be used in obstetrical operations (Please refer to section 4.6).

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, tachypnea, cyanosis, arrhythmias, and unstable blood pressure. (It should also be noted that many of these nonspecific signs may appear with light anesthesia, 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). PaO_2 and pH may decrease, and hyperkalemia and a base deficit may appear. Fatal outcome of malignant hyperthermia has been reported with isoflurane. 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.

Isolated cases of increased carboxyhemoglobin have been reported with the use of halogenated inhalation agents with a -CF_2H 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 manufacturers' instructions for CO_2 absorbents.

Rare cases of extreme heat, smoke and/or spontaneous fire in the anesthesia machine have been reported during administration of general anesthesia with drugs in this class when used in conjunction with desiccated CO_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.

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 postoperative period. Patients with latent as well as overt neuromuscular disease, particularly Duchenne muscular dystrophy, appear to be most vulnerable. Concomitant use of succinylcholine has been associated with most, but not all of these cases. These patients also experienced significant elevations in serum creatine kinase levels and, in some cases, changes in urine consistent with myoglobinuria. Despite the similarity in presentation to malignant hyperthermia, none of these patients exhibited signs or symptoms of muscle rigidity or hypermetabolic state. Early and aggressive intervention to treat the hyperkalaemia and resistant arrhythmias is recommended, as is subsequent evaluation for latent neuromuscular disease.

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 (please refer to section 4.7).

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

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.

4.5 Interaction with other medicinal products and other forms of interaction

The simultaneous administration of isoflurane and the following products requires strict supervision of the clinical and biological condition of the patient;

Combinations advised against:

- Beta-sympathomimetics (isoprenaline) and alpha- and beta-sympathomimetics (epinephrine or adrenaline; norepinephrine or noradrenaline): should be used with caution during isoflurane narcosis, due to a potential risk of ventricular arrhythmia.

- Nonselective MAOI: Risk of crisis and hemodynamic instability during the surgery or medical procedures. Treatment should be stopped 15 days prior to surgery.

Combinations requiring precautions in using:

- Beta-blockers: Concomitant use of beta blockers may exaggerate the cardiovascular effects of inhalational anesthetics, including hypotension and negative inotropic effects. Risk of blockage of the cardiovascular compensation mechanism, as a result of which negative inotropic effects are intensified. The action of beta-blockers can be suppressed during the operation with the use of beta-sympathomimetic agents. In general, any medication with a beta-blocker need not be stopped and an abrupt reduction of the dosage should be avoided.

- Isoniazid: Risk of potentiating the hepatotoxic effect, with increased formation of toxic metabolites of isoniazid. Treatment with isoniazid should be suspended one week before the operation and should not be resumed until 15 days afterwards.

- Epinephrine (adrenaline) by sub-cutaneous or gingival injections: risk of serious ventricular arrhythmia as a consequence of increased heart rate, although the myocardial sensitivity with respect to epinephrine is lower with the use of isoflurane than in the case of halothane. Thus, the dosage should be limited to, for example, 0.1 mg epinephrine within 10 minutes or 0.3 mg within one hour in adults. Doses of adrenaline greater than 5 mcg/kg, when administered submucosally, may produce multiple ventricular arrhythmias.

- 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.

- In the majority of cases where a drug treatment is indispensable, there is no reason to suspend it before general anaesthesia. It suffices to inform the anaesthetist about it.
- All commonly used muscle relaxants are markedly potentiated by isoflurane, the effect being most profound with non-depolarizing agents.

  Thus it is recommended that approximately one third to one half of the usual dose of these substances be administered. The disappearance of the myoneural effect takes longer with isoflurane than with other conventional anaesthetics. Neostigmine has an effect on the non-depolarising relaxants, but has no effect on the relaxing action of isoflurane itself.

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

– Calcium antagonists: isoflurane may lead to marked hypotension in patients treated with calcium antagonists, particularly dihydropyridine derivatives. Caution should be exercised when calcium antagonists are used concomitantly with inhalation anaesthetics due to the risk of additive negative inotropic effect.

  MAC (minimum alveolar concentration) is reduced by concomitant administration of N_2O 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 in pregnant women. Studies in animals have shown reproductive toxicity. Isoflurane should only be used during pregnancy if the benefit outweighs the potential risk (see section 5.3).

Isoflurane relaxes the uterus muscle, and the lowest possible concentration of isoflurane should be used in obstetrical operations.

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

Nursing Mothers
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

The medicinal product can have influence on driving and using machines. The patient should not drive or use machines for at least 24 hours after 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.

4.8 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 and liver adverse reactions (please refer to section 4.4 and 4.8). Shivering, nausea, vomiting and ileus have been observed in the postoperative period.

Cardiac arrest has been observed with general inhalation anesthetic 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 "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
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	Arrythmia
	Not known	Bradycardia
	Not known	Cardiac arrest
	Not known	Electrocardiogram QT prolonged
	Not known	Tachycardia
	Not known	Torsade de pointes
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
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
	Not known	Blood urea decreased
	Not known	Hyperthermia malignant[2]

General disorders and administration site conditions	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
	Not known	Blood alkaline phosphatase decreased
	Not known	Blood creatine phosphokinase increased
Musculoskeletal and connective tissue disorders	Not known	Myoglobinuria
	Not known	Rhabdomyolysis

[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 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 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 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 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 4.4)

During the induction of anesthesia, 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 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. Early and aggressive intervention to treat the hyperkalaemia and resistant arrhythmias is recommended, as is subsequent evaluation for latent neuromuscular disease (See 4.4).

Elderly:
Lesser concentrations of isoflurane are normally required to maintain surgical anesthesia in elderly patients. (See 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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il

4.9 Overdose
In case of overdosage, stop administration of the anaesthetic agent.

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. Check whether air passages are open, and depending on the circumstances, continue with assisted or controlled respiration using pure oxygen.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Isoflurane is an inhalation-type anaesthetic, belonging to the group of halogenated anaesthetics. Induction and recovery from anaesthesia take place rapidly with Isoflurane.

Isoflurane has the slightly irritating odour of ether, which can limit the speed of induction.

Pharyngeal and laryngeal reflexes are rapidly diminished as a result of which tracheal intubation is rendered easy.

5.2 Pharmacokinetic properties
Isoflurane is metabolised minimally in comparison to other halogenated anaesthetics.On average 95% of the Isoflurane is recovered in the expired air; 0.2% of the Isofluranethat is taken up within the body is metabolised. The principal metabolite is trifluoroacetic acid. The average serum level of inorganic fluoride in

patients administered Isoflurane anaesthesia is between 3 and 4 micromol/litre.

In patients anaesthetised with isoflurane, the mean serum concentration of inorganic fluorides is usually less than 5 micromol/litre and occurs about four hours after anaesthesia, returning to normal levels within 24 hours. This should not alter renal function in a normal subject.

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

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Isoflurane is supplied in 100 ml and 250 ml amber coloured glass bottles.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

See under section 4.2, Posology and Method of Administration.

7. MANUFACTURER

Piramal Critical Care INC., 3950, 18017, Pennsylvania. USA

8. REGISTRATION HOLDER

Pharma Medis Ltd., 4 Fireberg St., Holon, Israel

9. REGISTRATION NUMBER

105 52 28997 00

Revised in April 2022 according to MOH guidelines.