SCHEDULING STATUS: **S5**

PROPRIETARY NAME: **(and dosage form)**

ISOFOR Inhalation Anaesthetic

COMPOSITION:

ISOFOR inhalation anaesthetic contains isoflurane (1-chloro-2,2,2-trifluoro-ethyl difluoromethyl ether).

PHARMACOLOGICAL CLASSIFICATION:

A 2.1 Anaesthetics

PHARMACOLOGICAL ACTION:

ISOFOR is an inhalation anaesthetic with similar actions to those of halothane.

The properties of isoflurane allow smooth and rapid induction of, and emergence from, general anaesthesia. Induction of anaesthesia can be achieved in less than 10 minutes with an inhaled concentration of 3 % isoflurane in oxygen, and this concentration is generally reduced to 1,5 to 2,5 % for maintenance of anaesthesia. Induction is usually assisted by the injection of a rapidly acting barbiturate. The use of other adjuvant medicines, such as opioids, nitrous oxide and/or muscle relaxants, reduces the dose of volatile anaesthetic that is required to achieve the conditions optimal for surgery.

The clinical signs by which depth of anaesthesia are judged include progressive decreases in blood pressure and in respiratory volume and rate, as well as an increase in heart rate. When ventilation is controlled, changes in blood pressure and heart rate and responses to surgical stimulation are the most reliable indices. The pupils are small and responsive to light and are not a useful guide to depth of anaesthesia with isoflurane.

INDICATIONS:

General inhalation anaesthetic.

CONTRA-INDICATIONS:

Sensitivity to isoflurane or any related agent.

Patients with known or suspected susceptibility to malignant hyperpyrexia should not be anaesthetised with ISOFOR.

ISOFOR is best avoided in patients with space-occupying lesions or raised intracranial pressure as it is reported to increase cerebrospinal pressure.

Safety in pregnancy and lactation has not been established.

Isoflurane must not be used in patients who have developed an icterus and/or fever of unknown origin after administration of Isoflurane or other halogenated anaesthetics.

DOSAGE AND DIRECTIONS FOR USE:

Administer by inhalation. The use of Isoflurane-specific vaporisers will facilitate accurate control of the administered concentration of anaesthetic.

Isoflurane has a slight pungent ethereal odour, which may limit the rate of gas induction but, despite this, induction and particularly recovery are rapid.

Premedication:

Premedication medicines should be selected according to the needs of the patient. The ventilatory depressant effect of Isoflurane should be taken into account. Anticholinergic medicines (e.g. atropine, glycopyrrolate USP) may be used for their effects in drying oral secretions (antisialogogue) at the discretion of the anaesthesiologist, but they may enhance the weak effects of Isoflurane in increasing heart rate.

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. Salivation and coughing may be troublesome in small children induced with Isoflurane. 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 to 3,0 % usually produce surgical anaesthesia in 7 to 10 minutes. Blood pressure decreases during induction, but this may be compensated by surgical stimulation.

Maintenance:

Adequate anaesthesia for surgery may be sustained with an inspired Isoflurane concentration of 1,0 % to 2,5 % in an oxygen/70 % nitrous oxide mixture. Additional inspired Isoflurane (0,5 % to 1,0 %) will be required with lower nitrous oxide levels, or when Isoflurane is given with oxygen alone or with air/oxygen mixtures.

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

Excessive falls in blood pressure may be due to the depth of anaesthesia and, in such circumstances, can be corrected by reducing the inspired Isoflurane concentration.

Recovery:

The concentration of Isoflurane can be reduced to 0,5 % at the start of closing the operation wound, and then to 0 % at the end of surgery, provided that the anaesthesiologist is satisfied that the effect of any neuromuscular blocking medicines has been reversed and the patient is no longer paralysed.

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

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side-effects:

Adverse effects which may occur include involuntary muscle movements, hiccup, coughing, bronchospasm, laryngospasm, hypotension, cardiac arrhythmias, respiratory depression and emergence reactions. Shivering, nausea and vomiting have been reported in the postoperative period.

Malignant hyperpyrexia has been reported. The condition is familial and is often fatal. It is characterised by a rapid rise in body temperature usually accompanied by muscle rigidity and myoglobinuria. There may be cardiovascular changes, acidosis, and increases in serum-enzyme concentrations.

Induction with Isoflurane is not as smooth as with halothane and may be connected with pungency; coughing and laryngospasm may occur.

Other side-effects encountered while using Isoflurane are an increase in the white blood cell count (even in the absence of surgical stress).

Special Precautions:

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

Because levels of anaesthesia can be altered easily and quickly with Isoflurane, only vaporisers which produce a predictable concentration with a good degree of accuracy should be used. The degree of hypotension and ventilatory depression may provide some indication as to the level of anaesthesia. The level of anaesthesia may be changed quickly with Isoflurane.

Heart rhythm remains stable but spontaneous breathing should be monitored closely and supported where necessary.

Isoflurane causes an increase in cerebral blood flow at deeper levels of anaesthesia (1.5%) and this may give rise to an increase in cerebral spinal fluid pressure.

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

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

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

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

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

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

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

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

Patients with impaired function of the adrenal cortex, such as those who are being treated or have recently been treated with corticosteroids may experience hypotension with the stress of anaesthesia. Treatment with corticosteroids, pre-operatively and postoperatively, may be necessary.

Patients with chronic diseases such as diabetes or hypertension may require adjustment to therapy prior to anaesthesia. Anaesthetic agents should be used with caution in patients with cardiac, respiratory, renal or hepatic impairment.

Patients should not undertake hazardous tasks such as driving for at least 24 hours after a general anaesthetic.
Isoflurane relaxes the uterine muscle.

Interactions:
Patients taking long-term medication may require a change of dosage or cessation of therapy before major elective surgery. Such medications include aspirin, oral anticoagulants, oestrogens, monoamine oxidase inhibitors, and lithium.

Serious effects may follow the use of some agents administered as adjuncts to anaesthesia in patients taking, or having recently taken, some antidepressants.

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

Adrenaline: Administration of adrenaline (epinephrine) by any route, and some other ß-sympathomimetic medicines, during Isoflurane anaesthesia may cause supraventricular or ventricular arrhythmias.

Calcium Antagonists (and other Vasodilators): Isoflurane can cause marked hypotension in patients receiving concomitant therapy with calcium antagonists, especially those of the dihydropyridine class. Patients receiving chronic therapy with other vasodilators such as ACE inhibitors (e.g. captopril, enalapril, lisinopril) or a $^{1-}$ adrenoceptor antagonists (e.g. prazosin), may show unpredictable hypotension with any type of anaesthesia.

Narcotic Analgesics: The anaesthetic effect of Isoflurane can be potentiated by narcotic analgesics.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Refer to "Side-effects and Special Precautions".

Treatment is supportive and symptomatic.

IDENTIFICATION:

ISOFOR is a clear, bright, colourless liquid with a characteristic ethereal odour.

PRESENTATION:

ISOFOR is supplied in bottles of 100 ml and 250 ml

STORAGE INSTRUCTIONS:

Store below 25 °C.

Protect from light.

Keep tightly closed.

Keep out of reach of children.

REGISTRATION NUMBER:

28/2.1/0165

NAME AND BUSINESS ADDRESS OF APPLICANT:

Safeline Pharmaceuticals (Pty) Ltd

4845 Rugby Street, Weltevreden Park, Roodepoort

Tel 27 11 288 5360 Fax 27 11 288 5399

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

June 2005