SCHEDULING STATUS : **S5**

PROPRIETARY NAME (and dosage form)

SOJOURN™ Liquid

COMPOSITION

SOJOURN™ contains 250 ml Sevoflurane with no additives added.

Sevoflurane is chemically identified as Fluoromethyl 2,2,2-trifluoro-l- (trifluoromethyl) ethyl ether.

PHARMACOLOGICAL CLASSIFICATION

A 2.1 - Anaesthetics

PHARMACOLOGICAL ACTION

Sevoflurane is an inhalational anaesthetic agent for use in induction and maintenance of general anaesthesia.

Tracheobronchial tree secretions are not markedly stimulated. Sevoflurane depresses respiratory function and blood pressure in a dose-related manner. Sevoflurane is a dose-related cardiac depressant. Sevoflurane does not produce increases in heart rate at doses less than 2 MAC.

A study investigating the epinephrine (adrenaline) induced arrhythmogenic effect of sevoflurane versus isoflurane in adult patients undergoing transsphenoidal hypophysectomy demonstrated that the threshold dose of epinephrine (adrenaline) (i.e. the dose at which the first sign of arrhythmia was observed) producing multiple ventricular arrhythmias was

5 micrograms/kg with both sevoflurane and isoflurane. Consequently the interaction of sevoflurane with epinephrine (adrenaline) appears to be equal to that seen with isoflurane.

Animal studies have shown that blood flow (e.g. hepatic, renal, cerebral, coronary circulation) is well maintained with Sevoflurane.

Sevoflurane has minimal effect on neurodynamics or intracranial pressure and preserves $C0_2$ responsiveness.

Minimum Alveolar Concentration (MAC)

The minimum alveolar concentration (MAC) is the concentration in the lungs that is needed to prevent movement in 50 % of subjects in response to surgical stimulus. For MAC equivalents of sevoflurane for various age groups: (see dosage and directions for use.) The MAC of sevoflurane in oxygen was determined to be 2,05 % for a 40-year-old adult. MAC decreases with age and with the addition of nitrous oxide.

PHARMACOKINETICS

Solubility:

Because of the low solubility of sevoflurane in blood, the alveolar concentrations rapidly increase upon induction and rapidly decrease upon cessation of the inhaled agent. In a clinical study this was confirmed where inspired and end-tidal concentrations (F_1 and F_A) were measured.

The F_A / F_1 (washin) value at 30 minutes for Sevoflurane was 0,85. The $F_{A/}$ F_{AO} (washout) value at 5 minutes was 0,15.

Metabolism:

The rapid pulmonary elimination of sevoflurane minimises the amount of anaesthetic available for metabolism. In humans < 5 % sevoflurane absorbed is metabolised to hexafluoroisopropanol (HFIP), with release of inorganic fluoride and carbon dioxide (or a
one carbon fragment). Once formed HFIP is rapidly conjugated with glucuronic acid and eliminated. No other metabolic pathways for sevoflurane have been identified.

Fluoride Ion:

The defluorination of sevoflurane is not inducible by barbiturates.

INDICATIONS

SOJOURN™ is indicated for induction and maintenance of general anaesthesia in adult and paediatric patients for inpatient and outpatient surgery.

CONTRA-INDICATIONS

SOJOURN™ should not be used in patients with known hypersensitivity to Sevoflurane or to other halogenated agents or with known or suspected genetic susceptibility to malignant hyperthermia. Safety in pregnancy or lactation has not been established. (See Pregnancy and Lactation)

WARNINGS and SPECIAL PRECAUTIONS

Only persons trained in the administration of general anaesthesia should administer SOJOURN™. Facilities for maintenance of a patent airway, artificial ventilation, oxygen enrichment, and circulatory resuscitation must be immediately available**.**

Since the level of anaesthesia may be altered rapidly, only vaporizers producing predictable concentrations of SOJOURN™ and specifically calibrated for sevoflurane should be used.

Hypotension and respiratory depression increase as anaesthesia is deepened.

Malignant hyperthermia

Malignant hyperthermia: In susceptible individuals SOJOURN™ may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. The clinical syndrome is signaled by hypercapnia, and may include muscle rigidity, tachycardia, tachypnoea, cyanosis, arrhythmias, and/or unstable blood pressure. Some of these non-specific signs may also appear during light anaesthesia, acute hypoxia, hypercapnia and hypovolaemia. Treatment of malignant hyperthermia includes discontinuation of triggering agents, administration of intravenous

dantrolene sodium, and application of supportive therapy. Renal failure may appear later, and urine output should be monitored and sustained if possible.

General: During maintenance of anaesthesia, increasing the concentrations of SOJOURN™ produces dose-dependent decreases in blood pressure. Excessive decrease in blood pressure may be related to depth of anaesthesia and may be corrected by decreasing the inspired concentration of SOJOURN™. Maintenance of haemodynamic stability is important to the avoidance of myocardial ischaemia in patients with coronary artery disease.

The recovery from general anaesthesia should be assessed carefully before patients are discharged from the post-anaesthesia care unit.

Patients should be advised that performance of activities requiring mental alertness, such as operation of a motor vehicle or hazardous machinery, may be impaired for some time after general anaesthesia.

Renal Impairment: Because of the small number of patients with renal insufficiency (baseline serum creatinine greater than 0,133 mmol/litre studied the safety of SOJOURN™ administration in this group has not yet been fully established. Therefore, SOJOURN™ should be used with caution in patients with renal insufficiency.

Neurosurgery: In patients at risk for an increase in intracranial pressure, SOJOURN™ should be administered cautiously in conjunction with measures to reduce intracranial pressure (such as hyperventilation).

INTERACTIONS:

Barbiturates:

SOJOURN™ administration is compatible with barbiturates.

Benzodiazepines and Opioids :

Benzodiazepines and opioids would be expected to decrease the MAC of SOJOURN™ in the same manner as with other inhalational anaesthetics. SOJOURN™ administration is compatible with benzodiazepines and opioids as commonly used in surgical practice.

Nitrous oxide:

The MAC of SOJOURN™ is decreased when administered in combination with nitrous oxide. The MAC equivalent dose requirement is reduced approximately 50% in adult and approximately 25 % in paediatric patients.

Neuromuscular blocking agents:

SOJOURN™ increases both the intensity and duration of neuromuscular blockade induced by non-depolarising muscle relaxants. When SOJOURN™ is used to supplement alfentanyl N_2O anaesthesia it potentiates neuromuscular block induced with pancuronium, vecuronium
or atracurium. The effect of SOJOURN™ on the duration of depolarising neuromuscular blockade induced by succinylcholine has not been studied.

Dosage reduction of neuromuscular blocking agents during induction of anaesthesia may result in delayed onset of conditions suitable for endotracheal intubation or inadequate muscle relaxation because potentiation of neuromuscular blocking agents is observed a few minutes after the beginning of SOJOURN™ administration.

Among non-depolarising agents, only vecuronium, pancuronium and atracurium interactions have been studied during SOJOURN™ anaesthesia. In the absence of specific guidelines:

(1) for endotracheal intubation, do not reduce the dose of non-depolarising muscle relaxants,

(2) During maintenance of anaesthesia, the dose of non-depolarising muscle relaxants is likely to be reduced compared to that during N_2O/opioid anaesthesia. Administration of supplemental doses of muscle relaxants should be guided by the response to nerve stimulation.

PREGNANCY AND LACTATION

Pregnancy and Lactation: The safety of SOJOURN™ in pregnancy and lactation has not been established. SOJOURN™ may be used for anaesthesia during Caesarean section.

DOSAGE AND DIRECTIONS FOR USE

Pre-medication:

Pre-medication should be selected according to the need of the individual patient, and at the discretion of the anaesthesiologist.

Surgical-anaesthesia:

The concentration of SOJOURN™ being delivered from a vaporiser during anaesthesia should be known. This may be accomplished by using a vaporiser calibrated specifically for sevoflurane.

Induction:

Dosage should be individualised and titrated to the desired effect according to the patient's age and clinical status. A short acting barbiturate or other intravenous induction agent may be administered, followed by inhalation of SOJOURN™ . Induction with SOJOURN™ may be achieved in oxygen or in combination with oxygen-nitrous oxide mixtures. Inspired concentrations of up to 8 % SOJOURN™ usually produces surgical anaesthesia in less than 2 minutes in both adults and children.

Maintenance:

Surgical levels of anaesthesia can usually be achieved with concentrations of

0,5 – 3 % SOJOURN™ with or without the concomitant use of nitrous oxide.

Elderly: Lesser concentrations of SOJOURN™ are normally required to maintain surgical anaesthesia.

MAC Values for Adults and Paediatric Patients According to Age		
Age of Patient (years)	**Sevoflurane in Oxygen**	**Sevoflurane in 65 % N_2O/35 %O_2**
0-1 month *	3,3 %	
1- < 6 months	3,0 %	
6 months -< 3 years	2,8 %	2,0 % **
3 – 12	2,5 %	
25	2,6 %	1,4 %
40	2,1 %	1,1 %
60	1,7 %	0,9 %
80	1,4 %	0,7 %
*Neonates are full-term gestational age. MAC in premature infants has not been determined. ** In 3-< 5 year old paediatric patients, 60 % N_2O/40 %O_2 was used.		

Emergence:

Emergence times are generally short following SOJOURN™ anaesthesia. Therefore, patients may require postoperative pain relief earlier.

SIDE-EFFECTS

Cardiovascular disorders:

Frequent: Hypotension

Less frequent: Bradycardia, tachycardia, hypertension

In elderly patients:

Frequent: Bradycardia

Patients with renal or hepatic dysfunction are more likely to develop hypotension than the average patient.

Gastrointestinal disorders:

Frequent: Nausea and vomiting

Nervous system disorders:

Less frequent: Agitation, somnolence, dizziness and increased salivation

In paediatric patients:

Frequent: Agitation

The following have been reported but the frequency is unknown:

Cases of dystonic movement with spontaneous resolution, which have an uncertain relationship to SOJOURN™ have been reported in children receiving SOJOURN™ for induction of anaesthesia.

Respiratory system disorders:

Frequent: Increased cough

Less frequent: Respiratory disorder and laryngospasm.

In paediatric patients:

Frequent: Increased cough

Hepato-biliary:

Less frequent: Postoperative hepatitis

Other:

Less frequent: Fever, chills, hypothermia and headache, malignant hyperthermia (see WARNINGS and SPECIAL PRECAUTIONS)

The following have been reported but the frequency is unknown:

SOJOURN™ may cause dose-dependent cardio-respiratory depression.

Laboratory Test Results:

The following have been reported but the frequency is unknown:

- Transient elevations in glucose and white blood cell count may occur.
- Increases in serum inorganic fluoride levels may occur during and after SOJOURN™ anaesthesia.
- Concentrations of inorganic fluoride generally peak within 2 hours of the end of SOJOURN™ anaesthesia and return within 48 hours to preoperative levels. In clinical trials, elevated fluoride concentrations were not associated with impairment of renal function. Cases of transient changes in hepatic function tests were reported with SOJOURN™

KNOWN SYMPTOMS OF OVER DOSAGE AND PARTICULARS OF ITS TREATMENT

In the event of apparent over dosage, the following action should be taken:

Discontinue administration of SOJOURN™, maintain a patent airway, initiate assisted or controlled ventilation with oxygen and maintain adequate cardiovascular function.

IDENTIFICATION

SOJOURN™ is a clear, colourless liquid containing no additives or chemical stabilizer.

PRESENTATION

SOJOURN™ is supplied in 250 ml amber glass bottles.

STORAGE INSTRUCTIONS

Store at or below 25 °C.

Keep out of reach of children.

After opening the bottle close the cap tightly to avoid evaporation.

REGISTRATION NUMBER

41/2.1/0098

NAME AND ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Safeline Pharmaceuticals (Pty) Ltd

4845 Rugby Street, Weltevreden Park, 1715

South Africa

DATE OF PUBLICATION OF THE PACKAGE INSERT

December 2014

Manufacturer: **Piramal Critical Care, Inc.**

3950 Schelden Circle, Bethlehem

PA 18017, Made in the USA