SUMMARY PRODUCT CHARACTERISTICS (SPC)

1. NAME OF THE MEDICINAL PRODUCT

SEVO-SWISS 250 ML

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Bottle contains:
Sevoflurane USP……250 ml

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Liquid for Inhalation

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Sevoflurane is indicated for induction and maintenance of general anesthesia in adult and pediatric patients for inpatient and outpatient surgery.

4.2 Posology and method of administration

Premedication should be selected according to the need of the individual patient, and at the discretion of the anesthetist. ***Surgical Anesthesia:*** Sevoflurane should be delivered via a vaporizer specifically calibrated for use with sevoflurane so that the concentration delivered can be accurately controlled. MAC (minimum alveolar concentration) values for sevoflurane decrease with age and with the addition of nitrous oxide. The table below indicates average MAC values for different age groups.

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 sevoflurane. Induction with sevoflurane may be achieved in oxygen or in combination with oxygen-nitrous oxide mixtures. In adults inspired concentrations of up to 5%

sevoflurane usually produce surgical anaesthesia in less than 2 minutes. In children, inspired concentrations of up to 7% sevoflurane usually produce surgical anaesthesia in less than 2 minutes. Alternatively, for induction of anaesthesia in unpremedicated patients, inspired concentrations of up to 8% sevoflurane may be used.

Maintenance: Surgical levels of anaesthesia may be sustained with concentrations of 0.5 - 3% sevoflurane with or without the concomitant use of nitrous oxide. **Emergence:** Emergence times are generally short following sevoflurane anaesthesia. Therefore, patients may require early post-operative pain relief.

Use in Special Population: ***Pregnancy:*** Sevoflurane has a relaxant effect on the uterus, which can lead to increased uterine bleeding. Use during labour and delivery is limited to one small study in caesarean section. There are no adequate and well-controlled studies in pregnant women; therefore, sevoflurane should be used during pregnancy only if clearly needed.

Breastfeeding: It is not known whether sevoflurane or its metabolites are excreted in human milk. Due to the absence of documented experience, women should be advised to skip breast-feeding for 48 hours after administration of sevoflurane and discard milk produced during this period.

Labour and Delivery: In a clinical trial, the safety of sevoflurane was demonstrated for mothers and infants when used for anaesthesia during Caesarean section. The safety of sevoflurane in labour and vaginal delivery has not been demonstrated.

4.3 Contraindications

Sevoflurane should not be used in patients with known or suspected sensitivity to sevoflurane or other halogenated anaesthetics (e.g. history of liver function disorder, fever or leucocytosis of unknown cause after anaesthesia with one of these agents). Sevoflurane is also contraindicated in patients with known or suspected genetic susceptibility to malignant hyperthermia. Sevoflurane is

contraindicated in patients in whom general anaesthesia is contraindicated.

4.4 Special warnings and precautions for use

Sevoflurane 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. Sevoflurane should be administered only by persons trained in the administration of general anaesthesia. Facilities for maintenance ofa patent airway, artificial ventilation, oxygen enrichment and circulatory resuscitation must be immediately available. The concentration of sevoflurane being delivered from a vaporiser must be known exactly. As volatile anaesthetics differ in their physical properties, only vaporisers specifically calibrated for sevoflurane must be used. The administration of general anaesthesia must be individualised based on the patient's response. Hypotension and respiratory depression increase as anaesthesia is deepened.

Malignant Hyperthermia : In susceptible individuals, potent inhalation anaesthetic agents may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. The clinical syndrome is signalled by hypercapnia, and may include muscle rigidity, tachycardia, tachypnoea, cyanosis, arrhythmias, and/or unstable blood pressure. Some of these nonspecific signs may also appear during light anaesthesia, acute hypoxia, hypercapnia and hypovolaemia. Treatment includes discontinuation of triggering agents (e.g. sevoflurane), administration of intravenous dantrolene sodium (consult prescribing information for intravenous dantrolene sodium for additional information on patient management), 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 abnormalities. Renal failure may appear later, and urine flow should be monitored and sustained if possible.

Perioperative Hyperkalemia: 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 levelsand, 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. Isolated reports of QT prolongation, very rarely associated with torsade de pointes (in exceptional cases, fatal), have been received. Caution should be exercised when administering sevoflurane to susceptible patients. Isolated cases of ventricular arrhythmia were reported in paediatric patients with Pompe's disease. Caution should be exercised in administering general anaesthesia, including sevoflurane, to patients with mitochondrial disorders.

Hepatic: Very rare cases of mild, moderate and severe post-operative hepatic dysfunction or hepatitis with or without jaundice have been reported. Clinical judgment should be exercised when sevoflurane is used in patients with underlying hepatic conditions or under treatment with drugs known to cause hepatic dysfunction. Patients with repeated exposures to halogenated hydrocarbons, including sevoflurane, within a relatively short interval may have an increased risk of hepatic injury.

General: During the maintenance of anaesthesia, increasing the concentration of sevoflurane produces dose-dependent decreases in blood pressure. Excessive decrease in blood pressure may be related to depth of anaesthesia and in such instances may be corrected by decreasing the inspired concentration of sevoflurane. Particular care must be taken when selecting the dosage for patients who are hypovolaemic, hypotensive, or

otherwise hemodynamically compromised, e.g., due to concomitant medications. As with all anaesthetics, maintenance of haemodynamic stability is important to avoid myocardial ischaemia in patients with coronary artery disease. Caution should be observed when using sevoflurane during obstetric anaesthesia because the relaxant effect on the uterus could increase the risk of uterine bleeding. The recovery from general anaesthesia should be assessed carefully before patients are discharged from the recovery room. Rapid emergence from anaesthesia is generally seen with sevoflurane so early relief of postoperative pain may be required. Although recovery of consciousness following sevoflurane administration generally occurs within minutes, the impact on intellectual function for two or three days following anaesthesia has not been studied. As with other anaesthetics, small changes in moods may persist for several days following administration. Rapid emergence in children may be associated with agitation and lack of co-operation (in about 25% of cases).

Replacement of Desiccated CO2 Absorbents: Rare cases of extreme heat, smoke, and/or spontaneous fire in the anaesthesia machine have been reported during sevoflurane use in conjunction with the use of desiccated CO2 absorbent, specifically those containing potassium hydroxide (e.g Baralyme). An unusually delayed rise or unexpected decline of inspired sevoflurane concentration compared to the vaporiser setting may be associated with excessive heating of the CO2 absorbent canister. An exothermic reaction, enhanced sevoflurane degradation, and production of degradation products can occur when the CO2 absorbent becomes desiccated, such as after an extended period of dry gas flow through the CO2 absorbent canisters. Sevoflurane degradants (methanol, formaldehyde, carbon monoxide, and Compounds A, B, C, and D) were observed in the respiratory circuit of an experimental anaesthesia machine using desiccated CO2 absorbents and maximum sevoflurane concentrations (8%) for extended periods of time (≥ 2 hours). Concentrations of formaldehyde observed at the anaesthesia respiratory circuit (using sodium hydroxide containing absorbents) were consistent with levels known to cause mild respiratory irritation. The clinical relevance of the degradants observed

under this extreme experimental model is unknown. If a health care professional suspects that the CO2 absorbent has become desiccated, it must be replaced before subsequent use of volatile anaesthetics (such as sevoflurane). It must be taken into account that the colour indicator does not always change after desiccation has taken place. 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.

Renal Impairment: Because of the small number of patients with renal insufficiency (baseline serum creatinine greater than 1.5mg/dL) studied, the safety of sevoflurane administration in this group has not been fully established.

Therefore, sevoflurane should be used with caution in patients with renal insufficiency. In some studies in rats, nephrotoxicity was seen in animals exposed to levels of Compound A (pentafluoroisopropenyl fluoromethyl ether (PIFE)) in excess of those usually seen in routine clinical practice. The mechanism of this renal toxicity in rats is unknown and its relevance to man has not been established.

Neurosurgery & Neuromuscular Impairment: In patients at risk from elevation of intra-cranial pressure, sevoflurane should be administered cautiously in conjunction with techniques to lower intra-cranial pressure (e.g. hyperventilation).

Seizures: Rare cases of seizures have been reported in association with sevoflurane use. Use of sevoflurane has been associated with seizures occurring in children and young adults as well as older adults with and without predisposing risk factors. Clinical judgment is necessary before sevoflurane is used in patients at risk of seizures. In children the depth of anaesthesia should be limited. EEG may permit the optimization of sevoflurane dose and help avoid the development of seizure activity in patients with a predisposition for seizures.

Paediatric population: The use of sevoflurane has been associated with seizures. Many have occurred in children and young adults starting from 2 months of age, most of whom had no predisposing risk factors. Clinical judgment should be exercised when using sevoflurane in patients who may be at risk for seizures. Dystonic movements in children have been observed.

4.5 Interaction with other medicinal products and other forms of interaction

Beta-sympathomimetic agents like isoprenaline and alpha- and beta-sympathomimetic agents like adrenaline and noradrenaline should be used with caution during Sevoflurane narcosis, due to a potential risk of ventricular arrhythmia. Non-selective MAO-inhibitors: Risk of crisis during the operation. It is generally recommended that treatment should be stopped 2 weeks prior to surgery. Sevoflurane may lead to marked hypotension in patients treated with calcium antagonists, in particular dihydropyridine derivates. Caution should be exercised when calcium antagonists are used concomitantly with inhalation anesthetics due to the risk of additive negative inotropic effect. 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 pediatric patients during the post-operative period. Sevoflurane has been shown to be safe and effective when administered concurrently with a wide variety of agents commonly encountered in surgical situations such as central nervous system agents, autonomic drugs, skeletal muscle relaxants, anti-infective agents including aminoglycosides, hormones and synthetic substitutes, blood derivatives and cardiovascular drugs, including epinephrine.

Epinephrine/Adrenaline: Sevoflurane is similar to isoflurane in the sensitisation of the myocardium to the arrhythmogenic effect of exogenously administered adrenaline.

Indirect-acting Sympathomimetics: There is a risk of acute hypertensive episode with the concomitant use of sevoflurane

and indirect-acting sympathomimetics products (amphetamines, ephedrine).

Beta blockers: Sevoflurane may increase the negative inotropic, chronotropic and dromotropic effects of beta blockers (by blocking cardiovascular compensatory mechanisms).

Verapamil: Impairment of atrioventricular conduction was observed when verapamil and sevoflurane were administered at the same time.

Inducers of CYP2E1: Medicinal products and compounds that increase the activity of cytochrome P450 isoenzyme CYP2E1, such as isoniazid and alcohol, may increase the metabolism of sevoflurane and lead to significant increases in plasma fluoride concentrations. Concomitant use of sevoflurane and isoniazid can potentiate the hepatotoxic effects of isoniazid.

St John's Wort: Severe hypotension and delayed emergence from anaesthesia with halogenated inhalational anaesthetics have been reported in patients treated long-termwith St John's Wort.

Barbiturates: Sevoflurane administration is compatible with barbiturates as commonlyused in surgical practice.

Benzodiazepines and Opioids: Benzodiazepines and opioids are expected to decrease the MAC of sevoflurane in the same manner as with other inhalational anaesthetics. Sevoflurane administration is compatible with benzodiazepines and opioids as commonly used in surgical practice. Opioids such as alfentanil and sufentail, when combined with sevoflurane, may lead to a synergistic fall in heart rate, blood pressure and respiratory rate.

Nitrous Oxide: As with other halogenated volatile anaesthetics, the MAC of sevoflurane is decreased when administered in combination with nitrous oxide. The MAC equivalentis reduced approximately 50% in adult and approximately 25% in paediatric patients.

Neuromuscular Blocking Agents: As with other inhalational anaesthetic agents, sevoflurane affects both the intensity and duration of neuromuscular blockade by nondepolarising muscle relaxants.

When used to supplement alfentanil-N2O anaesthesia, sevoflurane potentiates neuromuscular block induced with pancuronium, vecuronium or atracurium. The dosage adjustments for these muscle relaxants when administered with sevoflurane are similar to those required with isoflurane. The effect of sevoflurane on succinylcholine and the duration of depolarising neuromuscular blockade 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 afew minutes after the beginning of sevoflurane administration.

Among non-depolarising agents, vecuronium, pancuronium and atracurium interactions have been studied. In the absence of specific guidelines: (1) for endotracheal intubation,do not reduce the dose of non-depolarising muscle relaxants; and, (2) during maintenance of anaesthesia, the dose of non-depolarising muscle relaxants is likely to be reduced compared to that during N2O/opioid anaesthesia. Administration of supplemental dosesof muscle relaxants should be guided by the response to nerve stimulation.

As with other agents, lesser concentrations of sevoflurane may be required following use of an intravenous anaesthetic e.g. propofol. Significant increases in plasma fluoride concentrations have been observed following the increased activity of CYP 2E1.

Effects on ability to drive and use machines: As with other agents, patients should be advised that performance of activities requiring mental alertness, such as operating a motor vehicle or hazardous machinery, may be impaired for some time after general anaesthesia. Patients should not be allowed to drive for a suitable period after sevoflurane anaesthesia.

4.6 Pregnancy and lactation

Pregnancy: Sevoflurane has a relaxant effect on the uterus, which can lead to increased uterine bleeding. Use during labour and delivery is

limited to one small study in caesarean section. There are no adequate and well-controlled studies in pregnant women; therefore, sevoflurane should be used during pregnancy only if clearly needed.

Breastfeeding: It is not known whether sevoflurane or its metabolites are excreted in human milk. Due to the absence of documented experience, women should be advised to skip breastfeeding for 48 hours after administration of sevoflurane and discard milk produced during this period.

Labour and Delivery: In a clinical trial, the safety of sevoflurane was demonstrated for mothers and infants when used for anaesthesia during Caesarean section. The safety of sevoflurane in labour and vaginal delivery has not been demonstrated.

4.7 Effects on ability to drive and use machines

As with other agents, patients should be advised that performance of activities requiring mental alertness, such as operating a motor vehicle or hazardous machinery, may be impaired for some time after general anaesthesia.

Patients should not be allowed to drive for a suitable period after sevoflurane anaesthesia.

4.8 Undesirable effects

Summary of the safety profile

As with all potent inhaled anaesthetics, sevoflurane may cause dose-dependent cardiorespiratory depression. Most adverse reactions are mild to moderate in severity and are transient in duration. Nausea, vomiting and delirium are commonly observed in the postoperative period, at a similar incidence to those found with other inhalation anaesthetics.

These effects are common sequelae of surgery and general anaesthesia which may be due to the inhalational anaesthetic, other agents administered intra-operatively or postoperatively and to the patient's response to the surgical procedure.

The most commonly reported adverse reactions were as follows : In adult patients: hypotension, nausea and vomiting.

In elderly patients: bradycardia, hypotension and nausea.

In paediatric patients: agitation, cough, vomiting and nausea.

Tabulated summary of adverse reactions : All adverse reactions at least possibly relating to sevoflurane from clinical trials and post-marketing experience are as below.The following frequency categories are used: Very common (≥1/10); common (≥1/100,<1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000,
<1/1,000); very rare (<1/10,000),including isolated reports. Post-marketing adverse reactions are reported voluntarily from a population with an unknown rate of exposure. Therefore it is not possible to estimate the true incidence of adverse events and the frequency is “unknown”. The type, severity and frequency of adverse reactions in sevoflurane patients in clinical trials were comparable to adverse reactions in reference-drug patients.

Immune system disorders

Unknown: Anaphylactic reaction, Anaphylactoid reaction, Hypersensitivity

Blood and lymphatic system disorders Uncommon: Leukopenia, Leukocytosis Psychiatric disorders

Very Common: Agitation Uncommon: Confusional state Nervous system

disorders Common: Somnolence, Dizziness, Headache Unknown: Convulsion,

Dystonia Cardiac disorders

Very Common: Bradycardia Common: Tachycardia

Uncommon: Atrioventricular block complete, Atrial fibrillation, Arrythmia, Ventricular extrasystoles, Supraventricular extrasystoles, Extrasystoles

Unknown: Cardiac arrest, QT prolongation associated with Torsade

Vascular disorders

Very Common: Hypotension Common: Hypertension

Respiratory, thoracic and mediastinal disorders

Very Common: Cough

Common: Respiratory disorder, Laryngospasm Uncommon: Apnoea, Hypoxia, Asthma

Unknown: Bronchospasm, Dyspnoea, Wheezing, Pulmonary oedema

Gastrointestinal disorders

Very Common: Nausea, Vomiting Common: Salivary hypersecretion Renal and urinary disorders

Uncommon: Urinary retention, Glycosuria Unknown: Renal failure acute

Hepato-biliary disorders

Unknown: Hepatitis, Hepatic failure, Hepatic necrosis

Skin and subcutaneous tissue disorders

Unknown: Dermatitis contact, Pruritus, Rash, Swelling face, Urticaria

Musculoskeletal and connective tissue disorders

Unknown: Muscle twitching

General disorders and administration site conditions

Common: Chills, Pyrexia, Hypothermia

Unknown: Chest discomfort, Hyperthermia malignant

Investigations

Common: Blood glucose abnormal, Liver function test abnormal, White blood cell count abnormal, Aspartate aminotransferase increased, Blood fluoride increased

Uncommon: Alanine aminotransferase increased, Blood creatinine

increased, Blood lactate dehydrogenase increased

Injury, poisoning and procedural complications

Common: Hypothermia

Description of selected adverse reactions

Transient increases in serum inorganic fluoride levels may occur during and after sevoflurane anaesthesia. Concentrations of inorganic fluoride generally peak within two hours of the end of sevoflurane anaesthesia and return within 48 hours to pre-operative levels. In clinical trials, elevated fluoride concentrations were not associated with impairment of renal function.

Rare reports of post-operative hepatitis exist. In addition, there have been rare postmarketing reports of hepatic failure and hepatic necrosis associated with the use of potent volatile anaesthetic agents, including sevoflurane. However, the actual incidence and relationship of sevoflurane to these events cannot be established with certainty. Rare reports of hypersensitivity (including contact dermatitis, rash, dyspnoea, wheezing, chest discomfort, swelling face, or anaphylactic reaction) have been received, particularly in association with long-term occupational exposure to inhaled anaesthetic agents, including sevoflurane. In susceptible individuals, potent inhalation anaesthetic agents may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia.

Paediatric population: The use of sevoflurane has been associated with seizures. Many of these have occurred in children and young adults starting from 2 months of age, most of whom had no predisposing risk factors. Clinical judgment should be exercised when using sevoflurane in patients who may be at risk for seizures.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after Authorisation 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 to the National

Regulatory Authority via Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org/

4.9 Overdose

In the event of overdosage, the following action should be taken: Stop drug administration, establish a clear airway and initiate assisted or controlled ventilation with pure oxygen and maintain adequate cardiovascular function.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMICS

Pharmacotherapeutic group: Anesthetics

ATC CODE -N01AB08

Cardiovascular Effects

As with all other inhalation agents sevoflurane depresses cardiovascular function in a dose related fashion. In one volunteer study, increases in sevoflurane concentration resulted in decrease in mean arterial pressure, but there was no change in heart rate. Sevoflurane did not alter plasma noradrenaline concentrations in this study.

Nervous System Effects

No evidence of seizure was observed during the clinical development programme. In patients with normal intracranial pressure (ICP), sevoflurane had minimal effect on ICP and preserved CO2 responsiveness. The safety of sevoflurane has not been investigated in patients with a raised ICP. In patients at risk for elevations of ICP, sevoflurane should be administered cautiously in conjunction with ICP-reducing manoeuvres such as hyperventilation.

5.2 PHARMACOKINETIC PROPERTIES

The low solubility of sevoflurane in blood should result in alveolar concentrations which rapidly increase upon induction and rapidly decrease upon cessation of the inhaled agent. In humans <5% of the absorbed sevoflurane is metabolised. The rapid and extensive

pulmonary elimination of sevoflurane minimises the amount of anaesthetic available for metabolism. Sevoflurane is defluorinated via cytochrome p450(CYP)2E1 resulting in the production of hexafluoroisopropanol (HFIP) with release of inorganic fluoride and carbon dioxide (or a one carbon fragment). HFIP is then rapidly conjugated with glucuronic acid and excreted in the urine.

The metabolism of sevoflurane may be increased by known inducers of CYP2E1 (e.g. isoniazid and alcohol), but it is not inducible by barbiturates. Transient increases in serum inorganic fluoride levels may occur during and after sevoflurane anaesthesia. Generally, concentrations of inorganic fluoride peak within 2 hours of the end of sevofluraneanaesthesia and return within 48 hours to pre-operative levels.

5.3 Preclinical safety data

None

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water For Injection

6.2 Incompatibilities

Not Applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30°C.

Keep out of reach and sight of children

6.5 Nature and contents of container

250 ml amber color glass bottle with black color cap with plastic plug and ring pull packed in a carton along with an insert.

7.0 MARKETING AUTHORIZATION HOLDER

Swiss Parenterals Ltd.

808, 809 & 810 Kerala Industrial Estate, G.I.D.C Near Bavla,

Dist: Ahmedabad 382 220, Gujarat, India

8.0 MARKETING AUTHORIZATION NUMBER

H2022/CTD9366/20549

9.0 DATE OF FIRST AUTHORIZATION

2023 September 06

10.0 DATE OF REVISION

2023 September 06