Proposed Professional Information for MILSIA 1% & 2 %

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

MILSIA 1 % 20 mL emulsion for injection/infusion

MILSIA 1 % 50 mL emulsion for injection/infusion

MILSIA 1 % 100 mL emulsion for injection/infusion

MILSIA 2 % emulsion for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

MILSIA 1 % 20 mL: Each vial contains 10 mg/mL propofol.

MILSIA 1 % 50 mL: Each vial contains 10 mg/mL propofol.

MILSIA 1 % 100 mL: Each bottle contains 10 mg/mL propofol.

MILSIA 2 %: Each vial contains 20 mg/mL propofol.

Sugar free.

Excipient with known effect:

Soybean oil, refined.

For the full list of excipients, see section 6 .1.

3. PHARMACEUTICAL FORM

Emulsion for injection/infusion.

A white milky emulsion, practically free from extraneous particulate contamination and large oil droplets.

The pH of the solution is between 7,5 and 8,5.

The osmolality is between 250 and 390 mOsmol/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MILSIA is indicated for:

- The induction and maintenance of general anaesthesia, as part of a balanced anaesthetic technique in patients over the age of three years.
- Sedation of ventilated adult patients receiving intensive care, for a period of up to 72 hours.
- Conscious sedation for diagnostic and surgical procedures in adults provided that there are adequate facilities for monitoring of haemodynamic and oxygenation parameters and if administered by a qualified anaesthetist.

4.2 Posology and method of administration

Posology:

Supplementary analgesic medicines are generally required in addition to MILSIA.

MILSIA has been used in association with spinal and epidural anaesthesia and with commonly used premedications, neuromuscular blocking medicines, inhalation and analgesic medicines; no pharmacological incompatibility has been encountered.

Dosage adjustment may be necessary when used together with the above medicines, particularly the narcotics (e.g. morphine, pethidine and fentanyl), combination of opioids and sedatives (e.g. benzodiazepines, barbiturates, droperidol, etc.), supplementary analgesic medicines (e.g. nitrous oxide or opioids) and the halogenated medicines (e.g. isoflurane, enflurane and halothane).

Where general anaesthesia with MILSIA is used simultaneously with a regional anaesthetic technique, lower doses of MILSIA may be required.

Dosage in ADULTS:

Induction of general anaesthesia:

MILSIA may be used to induce anaesthesia by bolus injection or infusion.

In unpremedicated and premedicated patients:

Most adult patients aged less than 55 years are likely to require 1,5 to 2,5 mg/kg of MILSIA, (approximately 40 mg every 10 seconds in an average healthy adult) by slow bolus injection or infusion titrated against the response of the patient until clinical signs show onset of anaesthesia:
The total dose required can be reduced by lower rates of administration (20 – 50 mg/minute).
Over the age of 55 years the requirements will generally be less.
In patients of ASA Grades lll and IV, lower rates of administration should be used (approximately 20 mg every 10 seconds).

Maintenance of general anaesthesia:

Anaesthesia can be maintained by administering MILSIA either by continuous infusion or by repeat bolus injections to prevent the clinical signs of light anaesthesia.

Continuous infusion:

The average rate of administration varies between patients, but rates in the region of 4 to 12 mg/kg/hour usually maintain satisfactory anaesthesia.
Slightly higher rates of administration may be required for 10 to 20 minutes after induction of anaesthesia.

Repeat bolus injections:

As a guide, increments of 25 mg to 50 mg may be used.

Sedation during intensive care:

To provide sedation for ventilated adult patients undergoing intensive care, it is recommended that MILSIA be given by continuous infusion, for up to 72 hours.

Adjust infusion rate according to the depth of sedation required. Rates of 0,3 - 4,0 mg/kg/hour should achieve satisfactory sedation. Rates above 4,0 mg/kg/hour are not recommended.

Conscious sedation for surgical and diagnostic procedures:

To provide sedation for surgical and diagnostic procedures, rates of administration should be individualised and titrated to clinical response.

Most patients will require 0,5 to 1 mg/kg over 1 to 5 minutes to initiate sedation. Maintenance of sedation may be accomplished by titrating MILSIA infusion to the desired level of sedation – most patients will require 1,5 to 4,5 mg/kg/hr. In addition to the infusion, bolus administration of 10 to 20 mg may be used if a rapid increase in the depth of sedation is required. In patients in ASA Grades Ill and IV, the rate of administration and dosage may need to be reduced.

Dosage in ELDERLY PATIENTS:

In elderly patients the dose requirements for induction of anaesthesia with MILSIA is reduced. The reduction should take account of the physical status and age of the patient. The reduced dose should be given at a slower rate and titrated against the response. Where MILSIA is used for maintenance of anaesthesia or sedation the rate of infusion or “target concentration” should also be reduced. Patients of ASA Grades III and IV, will require further reductions in dose and dose rate. Rapid bolus administration (single or repeated) should not be used in the elderly as this may lead to cardiorespiratory depression.

Dosage in CHILDREN:

MILSIA is not recommended for use in children less than 3 years of age (see section 4.3).

Induction of anaesthesia:

When used to induce anaesthesia, it is recommended that MILSIA should be titrated slowly until the clinical signs show the onset of anaesthesia. The dose should be adjusted for age and/or body weight. Most children over 8 years of age are likely to require approximately 2,5 mg of MILSIA per kg body weight for induction of anaesthesia. Under this age the dose requirement may be higher. Lower dosages are recommended for young patients at increased risk (ASA grades III and IV).

Maintenance of general anaesthesia:

Administer MILSIA by infusion to maintain the depth of anaesthesia required. The required rate of administration varies considerably between patients. 9 to 15 mg/kg/hour usually achieves satisfactory anaesthesia.

Sedation during intensive care:

MILSIA is not recommended for sedation in children as safety and efficacy have not been demonstrated. Although no causal relationship has been established, serious side effects (including fatalities) have been observed from spontaneous reports of unlicensed use. These events were seen most often in children with respiratory tract infections, given doses in excess of those recommended for adults. Associated findings include metabolic acidosis, lipaemia, rhabdomyolysis, cardiac irregularities and renal failure.

Conscious sedation for surgical and diagnostic procedures:

MILSIA is not recommended for conscious sedation in children as safety and efficacy have not been demonstrated.

Method of administration:

MILSIA 1 % may be used to induce anaesthesia by intravenous injection or infusion and bolus injection.

MILSIA 2 % may be used to induce anaesthesia by infusion only.

Administration of MILSIA 2 % by bolus injection is not recommended.

When MILSIA is used undiluted to maintain anaesthesia, it is recommended that equipment such as drop counters, syringe pumps or volumetric infusion pumps should always be used to control infusion rates. MILSIA can be used for infusion undiluted in glass infusion bottles or from plastic syringes.

MILSIA can be diluted with 5 % dextrose intravenous infusion only, in PVC infusion bags or glass infusion bottles.

It is recommended that, when using diluted MILSIA, the volume of 5 % dextrose removed from the infusion bag during the dilution process is totally replaced in volume by MILSIA emulsion.

Dilutions, which must not exceed 1 in 5 (2 mg propofol per ml), should be prepared aseptically immediately before administration and must be used within 6 hours of preparation.

The dilution may be used with a variety of infusion control techniques, but a giving set used alone will not avoid the risk of accidental uncontrolled infusion of large volume or diluted MILSIA. A burette, drop counter or volumetric pump must be included in the infusion line. The risk of uncontrolled infusion must be taken into account when deciding the maximum amount of MILSIA in the burette.

MILSIA may be administered via a Y-piece close to the injection site, into intravenous infusion of dextrose 5 %, sodium chloride 0,9 % or dextrose 4 % with sodium chloride 0,18 %.

MILSIA may be premixed with alfentanil injection.

In order to reduce pain on initial injection, that part of the MILSIA used for induction may be mixed with lignocaine (lidocaine) injection in the ratio of 20 parts MILSIA with up to 1 part of 1 % lignocaine (lidocaine) injection immediately prior to administration.

It is recommended that blood lipid levels be monitored routinely should MILSIA be administered to patients thought to be at particular risk of fat overload. Administration of MILSIA should be adjusted appropriately if the monitoring indicates that fat is being inadequately cleared from the body. If the patient is receiving other intravenous lipid concurrently, a reduction in quantity should be made in order to take account of the amount of lipid infused as part of the MILSIA formulation; 1,0 ml of MILSIA contains 0,1 g of fat.

Patients with hypovolaemia should have fluid-volume deficits corrected prior to administration of MILSIA.

For incompatibilities, refer to section 6.2.

In use precautions:

General:

Containers should be shaken before use.

MILSIA should be inspected for particulate matter and discolouration before administration.

Do not use if there is evidence of separation of the phases of the emulsion.

MILSIA contains no anti-microbial preservatives and the vehicle supports growth of micro-organisms.

When MILSIA is to be aspirated it must be drawn aseptically into a sterile syringe or giving set immediately after breaking the vial seal.

Administration must commence without delay.

Asepsis must be maintained for both MILSIA and infusion equipment throughout the infusion period.

Any infusion fluids added to the MILSIA line must be administered close to the cannula site.

MILSIA must not be administered via a microbiological filter.

Any container or syringe containing MILSIA is for single use in a single patient only.

General anaesthesia:

In accordance with established guidelines for other lipid emulsions a single infusion of MILSIA must not exceed 6 hours.

The syringe or giving set and any unused portion of MILSIA or solution containing MILSIA must be discarded at the end of the surgical procedure, or at 6 hours, whichever is the sooner, and replaced as appropriate.

Intensive care sedation:

Administration should commence promptly and must be completed within 12 hours after the vial has been spiked.

The tubing and any unused portion of MILSIA must be discarded after 12 hours.

If MILSIA is transferred to a syringe or other container prior to administration, the handling procedures for general anaesthesia (above) should be followed and the product should be discarded and

administration lines changed after 6 hours.

4.3 Contraindications

- Hypersensitivity to propofol or any ingredient of MILSIA (see section 6.1).
- MILSIA contains soya oil and egg lecithin, and should not be used in patients who are hypersensitive to peanuts, soya or eggs (see sections 4.4 and 6.1.
- MILSIA is contraindicated in children under the age of 3 years.
- Sedation of children of all ages with croup or epiglottitis receiving intensive care.

4.4 Special warnings and precautions for use

MILSIA should be given by those trained in anaesthesia (or, where appropriate, doctors trained in the care of patients in intensive care).

Respiration will be depressed and patients should be constantly monitored and facilities for maintenance of a patient airway, artificial ventilation, oxygen enrichment and other resuscitative facilities should be readily available at all times. MILSIA should not be administered by the person conducting the diagnostic or surgical procedure.

A generalised systemic reaction which may be anaphylactic in nature (including angioedema, bronchospasm, erythema and hypotension) may occur following MILSIA administration – estimated as 1 in 15 000.

EDTA is a chelator of metal ions, including zinc. The need for supplemental zinc should be considered during prolonged administration of MILSIA, particularly in patients who are predisposed to zinc deficiency, such as those with burns, diarrhoea and/or major sepsis.

MILSIA contains soya bean oil and egg lecithin and must not be used in patients with an allergy to peanuts, egg or soya protein (see section 4.3).

Abuse of, and dependence on MILSIA, predominantly by health care providers, have been reported (see section 4.8).

Administration of MILSIA:

The administration of MILSIA without airway care may result in fatal respiratory complications.

When MILSIA is administered for conscious sedation, for surgical and diagnostic procedures, patients should be continually monitored for early signs of hypotension, airway obstruction and oxygen desaturation.

MILSIA lacks vagolytic activity and has been associated with reports of bradycardia (occasionally profound) and also asystole. The intravenous administration of an anticholinergic medicine before induction, or during maintenance of anaesthesia should be considered, especially in situations where vagal tone is likely to predominate, or when MILSIA is used in conjunction with other medicines likely to cause a bradycardia.

During bolus administration for operative procedures, extreme caution should be exercised in patients with acute pulmonary insufficiency or respiratory depression.

As with other sedative medicines, when MILSIA is used for sedation during operative procedures, involuntarily patient movements may occur. During procedures requiring immobility these movements may be hazardous to the operative site.

During induction of anaesthesia, hypotension and transient apnoea may occur depending on the dose and use of premedicants and other medicines. Occasionally, hypotension may require use of intravenous fluids and reduction of the rate of administration of MILSIA during the period of anaesthetic maintenance.

MILSIA contains no antimicrobial preservatives and supports growth of micro-organisms.

When MILSIA is to be aspirated, it must be drawn aseptically into a sterile syringe or giving set immediately after breaking the vial seal. Administration must commence without delay. Asepsis must be maintained for both MILSIA and infusion equipment throughout the infusion period. Any infusion fluids added to the MILSIA line must be administered close to the cannula site. MILSIA must not be administered via a microbiological filter.
MILSIA is for single use in an individual patient. In accordance with established guidelines for other lipid emulsions, a single infusion or propofol must not exceed 12 hours. At the end of the procedure

or at 12 hours, whichever is the sooner, both the reservoir of propofol and the infusion line must be discarded and replaced as appropriate.

Clearance of MILSIA:

Caution should be applied in patients with cardiac, respiratory, renal or hepatic impairment or in hypovolaemic or debilitated patients. MILSIA clearance is blood flow dependent, therefore, concomitant medication that reduces cardiac output will also reduce MILSIA clearance.

Concomitant use:

Concomitant use of central nervous system depressants e.g., alcohol, general anaesthetics, narcotic analgesics will result in accentuation of their sedative effects. When MILSIA is combined with centrally depressant medicines administered parentally, severe respiratory and cardiovascular depression may occur. It is recommended that MILSIA is administered following the analgesic and the dose should be carefully titrated to the patient's response.

Patients should be instructed to avoid alcohol before and for at least 8 hours after administration of MILSIA.

Postoperative recovery from MILSIA:

An adequate period is needed prior to discharge of the patient to ensure full recovery after use of MILSIA. Very rarely the use of MILSIA may be associated with the development of a period of postoperative unconsciousness, which may be accompanied by an increase in muscle tone. This may or may not be preceded by a period of wakefulness. Although recovery is spontaneous, appropriate care of an unconscious patient should be administered.

MILSIA induced impairment is not generally detectable beyond 12 hours. The effects of MILSIA, the procedure, concomitant medications, the age and the condition of the patient should be considered when advising patients on:

- The advisability of being accompanied on leaving the place of administration
- The timing of recommencement of skilled or hazardous tasks such as driving
- The use of other medicines that may sedate (e.g. benzodiazepines, opiates, alcohol)

As with other anaesthetics, sexual disinhibition may occur during recovery.

Epileptic patients:

When MILSIA is administered to an epileptic patient, there may be a risk of convulsion.

Electroconvulsive treatment:

The use of MILSIA is not recommended with electroconvulsive treatment.

Mitochondrial disease:

Caution should be taken when treating patients with mitochondrial disease. These patients may be susceptible to exacerbations of their disorder when undergoing anaesthesia, surgery and ICU care. Maintenance of normothermia, provision of carbohydrates and good hydration are recommended for such patients. The early presentation of mitochondrial disease exacerbation and of the “propofol infusion syndrome” may be similar.

Advisory statements concerning intensive care unit (ICU) management:

Use of propofol emulsion infusions for ICU sedation has been
associated with a constellation of metabolic derangements and organ system failures that may result in death. Reports have been received of combinations of the following: metabolic acidosis, rhabdomyolysis, hyperkalaemia, hepatomegaly, renal failure, hyperlipidaemia, cardiac arrhythmia, brugada-type ECG (elevated ST-segment and coved T-wave) and rapidly progressive cardiac failure usually unresponsive to inotropic supportive treatment. Combinations of these events have been referred to as the “propofol infusion syndrome”. These events are mostly seen in patients with

serious head injuries and children with respiratory tract infections who received dosages in excess of those advised in adults for sedation in the ICU.

The following appear to be the major risk factors for the development of these events: decreased oxygen delivery to tissues; serious neurological injury and/or sepsis; high dosages of one or more of the following pharmacological medicines – vasoconstrictors, steroids, inotropes and/or MILSIA (usually at dose rates greater than 4 mg/kg/h for more than 48 hours).

Prescribers should be alert to these events in patients with the above risk factors and promptly consider decreasing or stopping the MILSIA dosage when the above signs develop. All sedative and therapeutic medicines used in the ICU, should be titrated to maintain optimal oxygen delivery and haemodynamic parameters. Patients with raised intra-cranial pressure should be given appropriate treatment to support the cerebral perfusion pressure during these treatment modifications.

Anaesthetists are reminded if possible, not to exceed the dosage of 4 mg/kg/h.

Appropriate care should be applied in patients with disorders of fat metabolism, patients predisposed of fat embolism and in other conditions where lipid emulsions must be used cautiously. Fat metabolism may be affected in conditions such as renal insufficiency, uncompensated diabetes mellitus, certain forms of liver insufficiency, metabolic disorders, severe trauma including long bone and multiple fractures, and sepsis.

It is recommended that blood lipid levels should be monitored if propofol is administered to patients thought to be at particular risk of fat overload (see section 4.2, “Method of administration”).
Lipids should be monitored in all patients if the duration of sedation is in excess of 3 days.

In the elderly, debilitated or ASA III or IV patients, rapid single or repeated bolus administration should not be used in order to minimise undesirable cardiorespiratory side effects.

Information on excipients of MILSIA:

MILSIA contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

Concomitant use of benzodiazepines, parasympatholytic medicines or inhalational anaesthetics has been reported to prolong the anaesthesia and to reduce the respiratory rate.

It is recommended that MILSIA be given after opioids so that the dose of MILSIA can be carefully titrated against the response.

After supplementary pre-medication of opiates, apnoea may occur with increasing frequency and over a prolonged period.

After administration of fentanyl, the blood level of MILSIA may be temporarily increased, with an increase in rate of apnoea.

The dosage of MILSIA should be reduced if used with nitrous oxide or halogenated anaesthetics.

Although MILSIA does not potentiate the effects of neuromuscular blockers, bradycardia and asystole have occurred after use of MILSIA with atracurium or suxamethonium.

When MILSIA is combined with centrally depressant medicines administered parenterally, severe respiratory and cardiovascular depression may occur.

Leucoencephalopathy has been reported with administration of lipid emulsions such as MILSIA in patients receiving ciclosporin.

Profound hypotension has been reported following anaesthetic with propofol in patients treated with rifampicin.

A need for lower doses has been observed in patients taking valproate. When used concomitantly, a dose reduction of MILSIA may be considered.

4.6 Fertility, pregnancy and lactation

Pregnancy:

The safety of MILSIA during pregnancy has not been established. MILSIA should not be used in pregnant women except when absolutely necessary. MILSIA crosses the placenta and may be associated with neonatal depression. MILSIA should not be used for obstetric anaesthesia unless clearly necessary.

Lactation:

MILSIA should not be used in mothers who are breastfeeding as it is distributed in breast milk for the first 24 hours after administration of MILSIA. Milk produced during this period should be discarded.

4.7 Effects on ability to drive and use machines

Patients should be advised that performance at skilled tasks, such as driving and operating machinery, may be impaired for some time after general anaesthesia. MILSIA induced impairment is not generally detectable beyond 12 hours.

4.8 Undesirable effects

System Organ Class	Frequency	Side Effects
Immune system disorders	Less frequent	Anaphylaxis which may include angioedema, bronchospasm, erythema and hypotension
Metabolism and nutrition disorders	Less frequent	Metabolic acidosis [2], hyperkalaemia [2]
	Frequency unknown	Hyperlipidaemia [2]

Psychiatric disorders	Less frequent	Euphoric mood, medicine abuse and drug dependence (see section 4.4)
Nervous system disorders	Frequent	Involuntary movements, headache during recovery phase
	Less frequent	Shivering or sensations of cold during recovery period, epileptiform movements, including convulsions and opisthotonos during induction, maintenance and recovery; post-operative unconsciousness that may be accompanied by an increase in muscle tone, dizziness
Cardiac disorders	Frequent	Tachycardia, bradycardia
	Less frequent	Cardiac dysrhythmia [2], cardiac failure sometimes with fatal outcome have been observed with doses exceeding 4 mg/kg/hour [2]
Vascular disorders	Frequent	Hypotension [5], hypertension
	Less frequent	Premature ventricular contractions, premature atrial contractions, syncope, abnormal ECG, ST segment depression, thrombosis and phlebitis
Respiratory, thoracic and mediastinal disorders	Frequent	Transient apnoea during induction, hiccups, coughing
	Less frequent	Pulmonary oedema, respiratory depression (dose dependent)

Gastrointestinal disorders	Less frequent	Nausea and vomiting during recovery phase, abdominal cramping, pancreatitis
Hepato-biliary disorders	Frequency unknown	Hepatomegaly [2]
Skin and subcutaneous tissue disorders	Less frequent	Tissue reactions experienced on accidental extravasation
Musculoskeletal and connective tissue disorders	Less frequent	Rhabdomyolysis [2 & 3]
	Frequency unknown	Dystonia, dyskinesia
Renal and urinary disorders	Less frequent	Discolouration of urine following prolonged administration
	Frequency unknown	Renal failure [2]
Reproductive system and breast disorders	Less frequent	Sexual disinhibition
General disorders and administration site conditions	Frequent	Local pain on induction [1], tingling, numbness or coldness at the injection site, excitation
	Less frequent	Tissue necrosis following accidental extravascular administration
	Frequency unknown	Local pain, swelling following accidental extravascular administration
Investigations	Less frequent	Brugada type ECG [2 & 4]
Injury, poisoning and procedural complications	Less frequent	Post-operative fever.

[1] Local pain at the injection site may be minimised by injection into a large vein and antecubital fossa or by co-administration of intravenous lignocaine (lidocaine). After co-administration of lignocaine (lidocaine) the following undesirable effects may occur: giddiness, vomiting, drowsiness, convulsions, bradycardia, cardiac dysrhythmia and shock.

[2] Combinations of these events, reported as “propofol infusion syndrome”, may be seen in seriously ill patients who often have multiple risk factors for the development of the events, see section 4.4).

[3] Reports of rhabdomyolysis have been received when MILSIA has been given at doses greater than 4 mg/kg/hr for ICU sedation.

[4] Brugada-type ECG – elevated ST-segment and coved T-wave in ECG.

[5] Marked hypotension may require use of intravenous fluids and a reduction in the rate of administration of MILSIA. Account should be taken of the possibility of severe drop in blood pressure in patients with impaired coronary or cerebral perfusion or those with hypovolaemia.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of MILSIA is important. It allows continued monitoring of the benefit/risk balance of MILSIA. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “**Adverse Drug Reactions Reporting Form**”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

See section 4.8.

Accidental overdosage is likely to cause cardiovascular and respiratory depression.

Respiratory depression should be treated by artificial ventilation with oxygen. Cardiovascular depression would require lowering of the patient's head, and, if severe, use of plasma expanders and pressor medicines. Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A.2.1 Central nervous system depressants: Anaesthetics.

Pharmacotherapeutic group: Other general anaesthetics.

ATC code: N01AC10.

Propofol (2,6-di-isopropylphenol) is a short acting anaesthetic given intravenously for the induction and maintenance of general anaesthesia. It is used for sedation in patients over the age of 16 years undergoing diagnostic procedures, in those undergoing surgery with local or regional anaesthesia, and in ventilated adult patients under intensive care. When used for anaesthesia, induction is rapid (approximately 30 seconds), as is recovery.

The mechanism of action is poorly understood. Falls in mean blood pressure and slight changes in heart rate are observed when propofol is administered for induction and maintenance of anaesthesia.

Ventilatory depression can occur following administration of propofol. Propofol reduces cerebral blood flow, intracranial pressure and cerebral metabolism. Recovery from anaesthesia is usually rapid and clear headed. Propofol has an anti-emetic effect. Propofol, at the concentrations likely to occur clinically, does not inhibit the synthesis of adrenocortical hormones.

5.2 Pharmacokinetic properties

Propofol is 98 % bound to plasma proteins.

The decline in propofol concentrations following a bolus dose, or following the termination of an infusion, can be described by a three compartment open model. The first phase is characterised by a rapid distribution (half-life 2 – 4 minutes), followed by rapid elimination (half-life 30 – 60 minutes) and a slower final phase, representative of redistribution of propofol from poorly perfused tissue.

Propofol is extensively distributed and rapidly cleared from the body (total body clearance 1,5 – 2 litres/minute).

Clearance occurs by metabolic processes, mainly in the liver, to form inactive conjugates of propofol and its corresponding quinol, which are excreted in the urine.

The pharmacokinetics are linear over the recommended range of infusion rates of propofol.

Under the usual maintenance regimens, significant accumulation of propofol does not occur.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Egg lecithin

Glycerol

Medium chain triglycerides

Refined soybean oil

Sodium hydroxide (for pH adjustment)

Sodium oleate

Water for injection.

6.2 Incompatibilities

MILSIA should not be mixed prior to administration with injections or infusion fluids other than 5 % dextrose or lignocaine (lidocaine) injection or alfentanil injection (see above).

The neuromuscular blocking medicines atracurium and mivacurium should not be given through the same intravenous line as MILSIA without prior flushing.

6.3 Shelf life

Unopened vials:

24 months.

After dilution:

Dilutions should be prepared aseptically immediately before administration and must be used within 6 hours of preparation.

6.4 Special precautions for storage

Store at or below 25 °C. Do not freeze. Shake well before use.

Discard any unused portion after 6 hours.

6.5 Nature and contents of container

MILSIA is presented in clear colourless glass vials (20 mL, 50 mL) or bottle (100 mL) with a grey bromobutyl rubber stopper crimped with a silver coloured aluminium cap and light blue polypropylene flip-off cap. The vials / bottles are placed in a carton with a package insert and patient information leaflet.

MILSIA is available in the following pack sizes:

MILSIA 1 % 20 mL: Carton containing 5 vials of 20 mL of emulsion for injection or infusion.

MILSIA 1 % 50 mL: Carton containing 1 vial of 50 mL emulsion for injection or infusion.

MILSIA 1 % 100 mL: Carton containing 1 bottle of 100 mL emulsion for injection or infusion.

MILSIA 2 %: Carton containing 1 vial of 50 mL emulsion for injection or infusion.

6.6 Special precautions for disposal and other handling

In use precautions:

Containers should be shaken before use.

Any portion of the contents remaining after use should be discarded.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd

Ground floor, Block K West, Central Park

400 16th road, Randjespark, Midrand 1685

South Africa

8. REGISTRATION NUMBERS

MILSIA 1 % 20 mL: A45/2.1/0701

MILSIA 1 % 50 mL: A45/2.1/0702

MILSIA 1 % 100 mL: A45/2.1/0703

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30 September 2016

10. DATE OF REVISION OF THE TEXT

06 April 2021 - SAHPRA approved 03 August 2021